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SUBACUTE BACTERIAL ENDOCARDITIS IN THE AGED

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INTRODUCTION

SUBACUTE bacterial endocarditis has actively engaged the attention of medical investigators ever since the clinical and pathologic studies of Osler,[1] Horder,[2] Billings,[3] Schottmueller,[4] and Libman and Celler,[5] taught physicians to differentiate the disease from other cardiac afflictions. Today, interest in this condition has been stimulated by the dramatic results achieved by Touroff[6] in the surgical treatment of patent ductus arteriosus complicated by bacterial endocarditis and by the remarkable success of Loewe and his collaborators[7] in the treatment of the disease with large doses of penicillin in combination with heparin. The present contribution is concerned with the occurrence of the disease in advanced age, hitherto but little emphasized, and attempts to define the clinical picture as modified by the manifestations of senescence and by various associated diseases. That bedside studies of old-age changes and the related maladies must be undertaken in terms of present day medicine has been emphasized elsewhere.[8] The need is urgent since the number of older individuals in the population is increasing so rapidly that the practitioner is more and more confronted by medical and surgical problems directly related to the advancing years.

My attention was first drawn to the problem of subacute bacterial endocarditis in the aged some fourteen years ago by a patient, 84 years of age, whose only symptoms were persistent severe backache and low-grade fever. More than a month passed before the possible value of a blood culture was realized. The recovery of *Streptococcus viridans* from the blood stream, on several occasions, made the diagnosis clear. The cardiac examination disclosed coarse systolic murmurs at the apex and at the base of the heart. Petechiae were noted only twice during the three months that he was under observation. Chills and night sweats became troublesome late in the illness, which terminated with signs pointing to cerebral embolism. Necropsy was not performed. Discussion of the case with colleagues at the time indicated that subacute bacterial endocarditis in the aged was not rare in their experience. Indeed, it appeared that more than one personage of note had fallen victim to this disease late in life.

Interest in the problem was re-awakened by the recent review of seven hundred post-mortem examinations of individuals 60 years old and over. These

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cases showed a surprisingly high incidence of both the acute and subacute varieties of bacterial endocarditis. The acute endocarditis group, comprising nine cases, has already been reported.[8] This communication is devoted to eighteen cases of subacute bacterial endocarditis in patients ranging from 60 to 87 years of age, which were observed on the wards of the Mt. Sinai Hospital during the past ten years. The age of 60 has been chosen as a minimum, partly because it is a convenient point of reference and partly because it represents a period of life when the aging process is usually well developed, having had its inception long before this.

The cases have been classified clinically according to the diagnostic problem involved, as follows:

Group A. Individuals presenting the typical, though often modified, clinical picture (nine cases).

Group B. Individuals in whom the diagnosis presents serious difficulties.

1. The bacteria-free cases (five cases).
2. Cases in which the diagnosis was completely obscured (four cases).

Tables I, II, and III summarize the salient clinical and pathologic features of these groups.

THE AGING OF THE CARDIOVASCULAR SYSTEM

The viewpoint of the ancients—that old age itself is a disease *(senectus ipsa est morbus)*—dominated medical thinking until about one hundred years ago, when, with increased knowledge, it became possible to differentiate many of the diseases that occur in advanced life. Today, the aging process and its inevitable end point, death, are considered essential properties of all living matter, and we can enumerate many of the fundamental structural and functional changes that characterize senescence. This has recently been well done by Carlson:[9]

"Progressive age changes not as yet shown to be due to specific diseases are: gradual tissue desiccation; gradual retardation of cell division, capacity of cell growth and tissue repair; gradual retardation in the rate of tissue oxidation; cellular atrophy, degeneration, increased cell pigmentation and fatty infiltration; gradual decrease in tissue elasticity and degenerative changes in the elastic connective tissue; decreased speed, strength and endurance of skeletal muscle; and progressive degeneration and atrophy of the nervous system; impaired vision, hearing, attention, memory and mental endurance."

While theoretically possible, death from old-age changes alone rarely, if ever, occurs. Death is always found to be the immediate result of some definite process.

In considering aging of the cardiovascular system we find that Cohn[10] has carefully described the gross and microscopic anatomic changes in the heart as well as its functional alterations. It is, however, clear from clinical experience that these changes, as Boas[11] emphasized, do not produce a clear-cut clinical picture, nor do they of themselves bring about a fatal issue. Actually the hearts of old people often show remarkably good functional capacity in spite of organic handicaps. This has been attested by Willius'[12] study of the hearts of seven hundred patients 75 years of age and older.

Arteriosclerosis was at one time regarded as an invariable concomitant, if not an essential part, of the aging process. That this is not true can be seen in any post-mortem room where the aged come to examination. The gross

diffuse vascular lesions commonly included in the term "arteriosclerosis" are conspicuously absent from the coronary arteries in as many as 30 per cent of old people.[13] Changes in the arteries properly ascribable to old age are to be correlated with those caused by mechanical, toxic, infectious, endocrine, metabolic, and neural agencies.

Since the association of increasing morbidity and mortality with advancing age is a commonplace of human experience which can be readily proved statistically,[14] we must look upon the structural and functional changes of senescence as providing the fertile soil, in which the most diverse diseases flourish singly and in combination with one another. So numerous are these morbid processes that the physician engaged in the treatment of old people finds it hard to differentiate clinically between so-called normal aging and its overgrowth of major maladies.

This difficulty will become clearer as we proceed with the study of subacute bacterial endocarditis, for here we shall see this disease flourish in association with many others. The question may well be posed: why do old people, who have had rheumatic heart disease for many years without symptoms, develop a secondary infection of the heart valves so late in life? Whether or not this lack of resistance to infection is to be regarded as an effect of the aging process is a problem that does not at present admit of ready solution.

LITERATURE

A review of the numerous papers on subacute bacterial endocarditis shows that nearly all the reported large series include cases in the higher age groups, but that, with several notable exceptions, no particular emphasis has been placed upon the older patients afflicted with the disease. In Blumer's[15] comprehensive review, published in 1923, he stated: "the figures indicate that subacute bacterial endocarditis is a disease of adolescents and young adults. In other words, the disease occurs during the period of greatest incidence of valvular heart disease, excluding the types due to syphilis and arteriosclerosis."

Clawson,[16] in 1924, reported 72 cases, of which nine occurred in the sixth decade, two in the seventh, and one in the eighth. Thayer,[17] in 1926, discussed 78 cases of which eleven occurred in the sixth and six in the seventh decade. Fulton and Levine,[18] in 1932, gave their findings in 111 patients, of whom the oldest was a man, 64 years of age. Hoff[19] in 1940, commenting on the clinical vagaries of endocarditis, described a group of five cases, characterized by progressive heart failure, which included a woman, 78 years of age; and a second group, characterized by a septic onset with symptoms of pneumonia and meningitis, of which one was a man, aged 60 years. Of thirteen patients, five were over 50 years of age.

Willius,[20] in 1940, presented the case of a man, aged 82 years, suffering from subacute bacterial endocarditis, and pointed out that the chief interest lay in the patient's age, since "in the vast majority of cases the patients are less than 50 years of age." The underlying valvular lesion was believed to be arteriosclerotic in nature.

In 1941, Christian,[21] in discussing the determinative background of the disease, emphasized the large number of young men affected, but took pains to point out that "subacute bacterial endocarditis cases occur in all age periods, and are not proportionately infrequent in the older groups, a fact that seems not to have been recognized very generally." Libman and Friedberg[22] in their monograph (1941) pointed out that "about two-thirds of the cases of subacute

TABLE I. CASES PRESENTING TYPICAL CLINICAL PICTURE

CASE	AGE (YRS.)	SEX	PREVIOUS RHEUMATIC HISTORY	BLOOD CULTURE	SIGNS OF VALVULAR DISEASE	EMBOLIC PHENOMENA	RENAL DISEASE	CLINICAL DIAGNOSIS	NECROPSY FINDINGS	MISCELLANEOUS FEATURES
1	60	F	14 years	*Enterococcus*	Mitral and aortic stenosis	Many petechiae, spleen palpable	Urine—red cells and albumin. Urea nitrogen, 16 mg.%	S.B.E.*	S.B.E. mitral valve with vegetation partially occluding orifice; rheumatic valvular disease, mitral and aortic stenosis, healed tricuspid valvulitis; focal embolic glomerulonephritis	Terminal clinical picture of extreme peripheral cyanosis and coldness suggested ball-thrombus of mitral valve
2	65	M	None	*Streptococcus viridans*	Systolic murmur at apex; diastolic murmur at left border of sternum	Embolic closure of right femoral artery, spleen palpable	Urine—albumin, red cells, casts. Urea nitrogen, 30 mg. %	S.B.E.	S.B.E. aortic valves mycotic aneurysm at base of aorta with fibrinous pericarditis. Syphilitic aortitis. Coronary artery sclerosis with marked narrowing of all branches. Multiple emboli in branches of inferior mesenteric artery	Wassermann reaction negative. No history of syphilis. Additional necropsy findings—healed duodenal ulcer, bilateral nephrolithiasis, marked diffuse arteriosclerosis
3	87	M	None	*Str. viridans*	Harsh systolic murmur at apex	Rare petechiae	Urine—albumin, no red cells	S.B.E.	S.B.E. mitral and aortic valves; moderate arteriosclerosis aortic and mitral valves; focal embolic glomerulonephritis; sclerosis of coronary arteries	Noteworthy are the age, the comparative well-being of patient for many weeks, and the minimal underlying arteriosclerotic changes in the valves
4	64	M	5 years	*H. parainfluenzae*	Harsh systolic murmur at apex	No petechiae. No clubbing of fingers	Urine—many red cells	S.B.E.	S.B.E. mitral valve and wall left auricle, rheumatic lesion mitral and tricuspid valves	Additional necropsy findings—focal embolic glomerulonephritis, left nephrolithiasis and chronic pyelonephritis
5	60	M	None	*Str. viridans*	Systolic murmurs	Rare pete-	Urine—albu-	S.B.E. sec-	----------	Healed osteomyelitis

*S.B.E. = Subacute bacterial endocarditis.

5	60	M	None	*Str. viridans*	Systolic murmurs at apex and base. Transient auricular fibrillation	Rare petechiae. Spleen palpable	Urine—albumin and red cells; urea nitrogen, 21 mg. %	S.B.E. secondary to arteriosclerotic heart disease	----------	Healed osteomyelitis of jaw; acute myocardial infarction 8 months before present illness. Not benefited by sulfonamides and hyperthermia
6	64	M	None	*Str. viridans*	Diastolic murmur at left border of sternum	Clubbing of fingers	Urine—many red cells	S.B.E. secondary to syphilitic heart disease	----------	Wassermann and Kahn reactions positive; on admission productive cough, malodorous sputum led to bronchoscopic and lipiodol demonstration of lower lobe bronchiectasis
7	74	M	None	*Str. viridans*	Coarse systolic murmur all over precordium	Clubbing of fingers	Urine—red cells. Urea nitrogen, 17 mg. %	S.B.E. secondary to teriosclerotic valvular lesions	----------	Fever and weight loss led to blood culture which was positive for *Str. viridans*. Sulfonamide therapy not tolerated
8	64	F	None	*Str. viridans*	Presystolic and systolic apical murmurs	Petechiae; spleen and liver palpable	Urine—albumin, casts, red cells. Urea nitrogen, 11 mg. %	S.B.E. secondary to rheumatic and arteriosclerotic heart disease	S.B.E. mitral valve; rheumatic valvular disease, mitral valve, bronchopneumonia, L.L.L., focal glomerulonephritis	X-ray of chest suggested mitral valve calcification. Electrocardiogram showed evidence of myocardial damage. Not benefited by sulfonamide therapy and hyperthermia
9	61	M	None	*Str. viridans*	Mitral and aortic insufficiency	Occluding petechiae; liver and spleen palpable. No clubbing	Urine—albumin and small numbers red cells. Urea nitrogen, 18 mg. %	S.B.E	Congenital septal defect with superimposed S.B.E. extending to right aortic cusp with perforation and to septal leaflet of tricuspid valve	Correct clinical diagnosis of S.B.E. but underlying cardiac defect not suspected, although apical heart sounds were obscured by murmur and phonocardiogram showed atypical group of murmurs

TABLE II. CASES IN THE BACTERIA-FREE STAGE

CASE	AGE (YRS.)	SEX	PREVIOUS RHEUMATIC HISTORY	BLOOD CULTURE	SIGNS OF VALVULAR DISEASE	EMBOLIC PHENOMENA	RENAL DISEASE	CLINICAL DIAGNOSIS	NECROPSY FINDINGS	MISCELLANEOUS FEATURES
10	63	M	None	Sterile	Presystolic at apex; harsh systolic at apex and aortic area	Petechiae; clubbing of fingers; liver and spleen palpable	Urea nitrogen, 91 mg. %	Not made	S.B.E. aortic valve; mitral and aortic stenosis (rheumatic); chronic glomerulonephritis; coronary sclerosis with narrowing; left pyonephrosis with large calculus; cholelithiasis, choledocholithiasis, and hepatic lithiasis	Gradual onset with weakness and fever for 6 months before death. Death due to right ventricular failure
11	64	F	Since childhood	3 cultures (3 weeks before death) sterile	Heart enlarged; long blowing systolic murmur over precordium; auricular fibrillation	No petechiae; marked hepatosplenomegaly	Urea nitrogen, (3 weeks before death), 50 mg. % Urine—fixed specific gravity; occasional red cells	Possibility of bacteria-free S.B.E. strongly considered. Hemoglobin, 42%; R.B.C. 2,500,000; W.B.C. 3,500 with normal differential	S.B.E. aortic and mitral valves with partial calcification of vegetations; chronic rheumatic heart disease, mitral, aortic, and tricuspid valves. Massive focal embolic glomerulonephritis	Four weeks before death observed in hospital for one week. Three weeks later readmitted with muscular twitching, emesis, epistaxis, and increased weakness. Died in twenty-four hours

12	74	M	None	Not done	Poor heart sounds; aortic diastolic murmur; congestion at lung bases; hepatic enlargement	Splenomegaly; no petechiae observed	Urine—much albumin; many red cells and white cells, with casts. Urea nitrogen, 37 mg. %; rose to 83 mg. %	Correct diagnosis not suspected	S.B.E. aortic valve with perforation of cusp; calcium in vegetations; chronic rheumatic valvular disease, mitral insufficiency; aortic stenosis	Correct diagnosis obscured by picture of renal insufficiency. Blood culture probably would have been sterile. Right ventricular failure important factor in fatal outcome
13	60	M	25 years	Not done	Cardiac enlargement; mitral and aortic lesions; congestive heart failure	No petechiae. Marked hepatosplenomegaly	Urea nitrogen, 58 mg. %; rose to 102 mg. %. marked anemia, hyperproteinemia	Rheumatic heart disease; chronic nephritis; cirrhosis of liver	S.B.E. aortic valve-perforation of cusp; rheumatic heart disease; mitral and aortic stenosis; glomerulonephritis, cirrhosis of liver	Advanced cardiac failure aggravated by anemia, and presence of uremia obscured signs pointing to S.B.E.
14	62	F	15 years	Sterile on three occasions	Cardiac enlargement; systolic murmur at apex and base; enlarged liver and spleen. Electrocardiogram indicated myocardial damage	Petechiae; clubbing of fingers	Urine, red blood cells. Urea nitrogen, 21 mg. %	S.B.E. in bacteria-free stage	----------	Absence of renal insufficiency and anemia does not exclude S.B.E. in bacteria-free stage. Discharged unimproved

TABLE III. CASES IN WHICH DIAGNOSIS WAS COMPLETELY OBSCURED

CASE	AGE (YRS.)	SEX	PREVIOUS RHEUMATIC HISTORY	BLOOD CULTURE	SIGNS OF VALVULAR DISEASE	EMBOLIC PHENOMENA	RENAL DISEASE	CLINICAL DIAGNOSIS	NECROPSY FINDINGS	MISCELLANEOUS FEATURES
15	70	F	None	Not done	Cardiac enlargement; aortic diastolic murmur; B.P. 210/90; auricular flutter	No petechiae	Urea nitrogen, 41 mg. %	Graves' disease with secondary thyrotoxic heart disease and heart failure	S.B.E. mitral, aortic, and tricuspid valves; chronic rheumatic valvular disease, mitral, aortic, tricuspid; coronary artery sclerosis; multiple colloid adenomata of thyroid; focal embolic glomerulonephritis	Graves' disease, thyrotoxic and rheumatic heart disease obscured signs of endocarditis
16	62	F	None	Not done	Tachycardia, systolic murmur at apex and base	No petechiae, palpable spleen	Urine—albumin and casts	Right hemiplegia due to cerebral hemorrhage	S.B.E. mitral valve; emboli, spleen, kidney, brain; acute fibrinous pericarditis; old occlusion right coronary artery; aneurysm left ventricle, acute myomalacia, myocardial fibrosis	That cause of hemiplegia was embolic was never suspected. Persistent low-grade fever and palpable spleen were disregarded

17	62	M	None	Six cultures made of which only the fifth showed *Str. viridans*	Cardiac enlargement; systolic and diastolic murmurs at apex and base; electrocardiogram showed bundle branch block	Petechiae noted once; clubbing of fingers	Urine—red cells. Urea nitrogen rose from 25 mg. % to 37 mg. %	Arteriosclerotic heart disease; acute purulent parotitis	S.B.E. mitral and aortic valves with calcification; rheumatic valvular disease, aortic and mitral stenosis; bicuspid aortic valve; old incomplete occlusion of left coronary artery; aneurysm left ventricle. Diffuse arteriosclerosis	Arteriosclerotic heart disease, with complicating parotitis obscured correct diagnosis
18	62	M	None	Not done	Cardiac enlargement; systolic murmur at apex; B.P., 178/100	No petechiae	Urine—albumin and red cells	Possible gastrointestinal malignancy	S.B.E. mitral and aortic valves, wall of left auricle; chronic rheumatic valvular disease, mitral and aortic	Weight loss, rapid sedimentation rate and constipation led to suspicion of malignant gastrointestinal lesion. Ruled out after x-ray and sigmoidoscopy. Further investigation barred by sudden death after transfusion

bacterial endocarditis occur in the third and fourth decades of life. Less commonly, however, the disease affects persons at any age of life from early childhood to old age."

Two statistical studies on the age incidence of disease are of great interest. Hedley,[23] who studied rheumatic heart disease in Philadelphia, found, in the five-year period from Jan. 1, 1930, to Dec. 31, 1934, 288 fatal cases of subacute bacterial endocarditis, of which thirty, or 10.4 per cent, occurred in persons over 50 years of age. Of these, five patients, or 1.7 per cent of the total, were over 60 years of age. Of the thirty cases, fourteen were secondary to rheumatic heart disease, the remainder to other forms of cardiac disease. The author's only comment on these older patients is: "all students of this problem with possible exception of Thayer observed that subacute bacterial endocarditis is infrequent during the age period under ten years and among persons over 60 years of age."

Gelfman[24] has recently reported on the incidence of acute and subacute bacterial endocarditis in fatal rheumatic heart disease from two Boston hospitals. Of great significance for the student of the heart in old age is his finding that, of 452 cases of rheumatic heart disease, 78, or 17.3 per cent, occurred in patients 60 years old and over. Of the 452 patients, 115 or 25.4 per cent, suffered also from acute and subacute bacterial endocarditis. Of these 115 patients, eight, or 6.9 per cent, were over 60 years of age, five cases occurring in the seventh, two in the eighth and one in the ninth decade.

These statistical reports demonstrate that the recognized incidence of the disease in old age is considerable. It is probable, however, that many cases of subacute bacterial endocarditis escape recognition because of the difficulties in diagnosis and also because sick old people are not often sent to hospitals where the correct diagnosis may be disclosed at necropsy. An additional factor is the tendency on the part of physicians to ascribe all the complaints of old persons to some manifestation of arteriosclerosis.

That considerable confusion exists even among pathologists is indicated by Denman's analysis,[25] in 1942, of fifty autopsied cases of subacute bacterial endocarditis. Following the table of age incidence, which includes five cases in patients ranging from 51 to 60 years of age, Denman states: "Six more cases were seen, but were excluded from this series because of their age and the possibility that their infectious endocarditis was a terminal manifestation rather than the primary cause of death. Their ages were 59, 66, 67 (two), 75 and 78 years."

The sole specific contribution to the problem of endocarditis in the aged has been made by Bayles and Lewis,[26] in 1940, who reported twenty-eight patients ranging from 40 to 72 years in age. The correct clinical diagnosis was made in only one-half of their cases. The most common pre-existing heart disease was rheumatic, occurring in 57 per cent, but arteriosclerotic, syphilitic, and congenital lesions (bicuspid aortic valves) were also present. They emphasize that the clinical features are essentially the same as in young patients but less accentuated: heart failure and azotemia are more common; demonstrable bacteriemia is less common. They conclude: "Subacute bacterial endocarditis occurs more frequently than suspected or heretofore reported in older individuals." In addition they suggest that, if the lives of patients with rheumatic heart disease be prolonged by more efficient care, the complication of subacute bacterial endocarditis may be more frequently postponed to their later years.

PATHOLOGY

Of the eighteen cases discussed in this paper, the fourteen which were examined at necropsy form the basis of the pathologic discussion. The principal etiological types of heart disease are represented in this group and furnish the foundation for the endocardial lesions. Congenital heart disease was present in one subject (Case 9), syphilitic in one (Case 2), thyrotoxic in one (Case 15), rheumatic in ten (Cases 1, 4, 8, 10, 11, 12, 13, 15, 17, and 18), and arteriosclerotic in seven (Cases 2, 3, 8, 10, 15, 16, and 17). Multiple etiological types were present in five of these cases: syphilis and arteriosclerosis occurring together in Case 2; rheumatic lesions and arteriosclerosis in Cases 8 and 10; and arteriosclerotic, rheumatic, and thyrotoxic changes in Case 15.

The incidence of clearly demonstrable old rheumatic valvular changes in ten of the fourteen autopsied cases is noteworthy in a group of patients over 60 years of age and is to be compared with Gelfman's Boston series.[24] Increasing emphasis by other writers shows that the occurrence of rheumatic heart disease in the aged must be regarded as considerable. White and Bland[27] have reported cases of rheumatic heart disease occurring in aged individuals. In the case of Rakov and Taylor,[28] a woman, 61 years old, was found at necropsy to have suffered from extensive acute rheumatic myocarditis, the entire myocardium being diffusely infiltrated by large numbers of Aschoff bodies. Attacks of paroxysmal nocturnal dyspnea, associated with congestive heart failure, were the outstanding clinical features in this case.

The occurrence of syphilis as an etiological agent in subacute endocarditis in the aged has been emphasized by Bayles and Lewis.[26] In Case 2, syphilitic aortitis and valvulitis were demonstrable at post-mortem examination, but for the true incidence in this series we must add Case 6, in which the diagnosis was well established on clinical grounds.

Some diversity of opinion exists as to the relationship of endocarditis to syphilitic aortitis and valvulitis. Smith,[29] reporting on the co-existence of syphilis of the aorta and bacterial endocarditis, presents two cases of acute and one of subacute endocarditis accompanied by syphilitic aortitis. In only one of these does he believe that the endocarditis was engrafted on a syphilitic valvulitis; in the second case the endocardial lesion occurred on undamaged valves, and, in the last, it was based on a rheumatic valvulitis. Boyd[30] believes that bacterial endocarditis superimposed on syphilitic valvulitis occurs more frequently than the literature would indicate. In 105 cases of bacterial endocarditis, he found fourteen to be definitely satisfactory examples of vegetative endocarditis superimposed on old syphilitic aortic valve disease. Koletsky[31] studied five cases with the diagnosis of cardiovascular syphilis and bacterial endocarditis. In four of these, stigmas of rheumatic fever were present, and in the fifth the endocarditis was engrafted on a normal aortic valve. My observations do not support the belief that syphilis is a significant predisposing factor in bacterial endocarditis.

The finding of congenital heart lesions in individuals who are advanced in years will not surprise anyone familiar with the work of Abbott.[32] The conditions described in her acyanotic and *cyanose tardive* groups are compatible with a fairly long life. In Touroff's series[6] of cases of patent ductus arteriosus complicated by subacute bacterial endocarditis, he reports two patients, one of 51 years, and the other 63 years. He points out: "Subacute bacterial endocarditis may occur at any age and constitutes a perpetual threat to the patient with a patent ductus arteriosus. . . . The patient with a patent ductus arteriosus should

be kept under observation throughout life, and a blood culture taken promptly if fever obscure in origin occurs.'' Uhley[33] has described Lutembacher's syndrome (interatrial septal defect and mitral stenosis) occurring in a man, aged 60 years, and mentions several other cases in older patients.[34]

In Case 9 of this series, a congenital defect of the interventricular septum *(maladie de Roger)* was found at necropsy. The patient was a 61-year-old man, who had no previous history of heart disease. Superimposed upon this typically located small defect were the lesions of subacute bacterial endocarditis, which had extended to involve and perforate the right aortic cusp and had also been implanted on the septal leaflet of the tricuspid valve. In Abbott's statistical analysis of 1,000 cases[32] of congenital heart disease, we find fifty cases of interventricular defect. The ages of the patients range from fetus to 49 years, and death is ascribed to bacterial endocarditis or endarteritis in thirteen cases.

Case 17 which exhibited a bicuspid aortic valve, is not included in the congenital group, since frank rheumatic lesions of the mitral valve were also present. Koletsky[35] has recently investigated the significance of bicuspid aortic valves in relation to bacterial endocarditis, confirming the views of Gross[36] that these valve changes are nearly all acquired and of rheumatic origin, and that this etiological factor explains their frequent association with superimposed endocarditis.

The mitral valve was involved by rheumatic changes in ten cases and by arteriosclerosis in two cases. Subacute bacterial endocarditis was engrafted on both arteriosclerotic valves, but only on eight of the ten rheumatic valves. The aortic valve was involved by rheumatism in eight cases, by syphilis in one case, and by arteriosclerosis in one case. Subacute bacterial endocarditis was found on the aortic valves ten times, in seven cases secondary to rheumatism and in one case each secondary to syphilis, to arteriosclerosis, and to congenital septal defect.

The aortic and mitral valves were simultaneously affected by rheumatic changes in eight cases, by arteriosclerotic changes in one case, and by subacute bacterial endocarditis in five cases. The tricuspid valve was the site of rheumatic changes in four cases, but of subacute bacterial endocarditis in only one of them. In Case 9 the tricuspid valve was secondarily involved by the vegetation arising in the interventricular septal defect.

As might be anticipated in a group of patients 60 years old and over, arteriosclerotic changes of marked degree were found in the hearts. Arteriosclerotic lesions of the valves were the site of vegetative endocarditis in only two instances (Cases 3 and 16). In four instances (Cases 2, 3, 10, and 15) marked coronary artery sclerosis was noted. In Case 16 the following changes were found: old occlusion of the right coronary artery, aneurysm of the left ventricle, acute myomalacia, and myocardial fibrosis; in Case 17, old incomplete occlusion of left coronary artery, and aneurysm of left ventricle. In this last case the clinical picture of subacute bacterial endocarditis was masked by the arteriosclerotic heart disease. In Case 16 the clinical picture was dominated by hemiplegia of embolic origin. In Case 14, not autopsied, the electrocardiogram indicated myocardial damage. Case 5 had suffered typical myocardial infarction six months before the diagnosis of endocarditis was made.

These findings indicate that even in old age rheumatic valvular lesions are the most important predisposing cause for localization of subacute endocardial inflammation. In our previous paper,[8] a similar conclusion was reached for acute bacterial endocarditis. Arteriosclerotic valvular lesions seem to be numerically less significant. On the other hand, arteriosclerosis of the coronary vessels

occurred in six of the thirteen cases, often associated with severe myocardial damage, and thus assumes importance by influencing the clinical picture, tending to obscure the presence of the endocarditis.

The cardiac lesions associated with sclerosis of the coronary vessels resulting in acute and chronic changes in the myocardium may have another pathogenic relationship to bacterial endocarditis. Keefer[37] has emphasized the occurrence of nonbacterial thrombotic endocarditis[38] in a variety of chronic diseases, including chronic heart disease, leucemia, cancer, and chronic pulmonary tuberculosis, and believes that these sterile platelet thrombi furnish favorable sites for the localization of bacteria. The experimental work of Nedzel[39] also has direct bearing on the pathogenesis of endocarditis in general and particularly in the aged. This worker studied, in dogs, the effect on the heart valves of pressor episodes artificially induced by injections of pitressin and found that by this method he could produce changes in the valvular endothelium and the subendothelial tissues which resembled, at first, nonbacterial and, later, bacterial endocarditis. He relates these artificial and highly exaggerated vascular spasms to those disturbances of splanchoperipheral balance occurring in human beings as the result of unusual changes in the meteorologic environment. The fundamental cause of the tissue changes, according to Nedzel, is local tissue anoxia of varying intensity. If these experimental studies are valid, they give us insight into the way in which nonbacterial thrombotic endocarditis may arise in a variety of serious diseases, and into the mechanism by which these primary lesions become secondarily infected.

In addition to the association of endocarditis with marked cardiac arteriosclerosis, certain other concomitant pathologic features of these cases are noteworthy. In Case 1 the terminal clinical picture of extreme peripheral cyanosis and coldness of the extremities suggested the diagnosis of ball-thrombus in the left auricle. Post-mortem examination revealed that the mitral valve vegetation was large enough to partially occlude the mitral orifice and had the same effect as a free ball-thrombus. In Case 2, where subacute bacterial endocarditis was engrafted on syphilitic aortitis and valvulitis, a mycotic aneurysm was present at the base of the aorta with an overlying fibrinous pericarditis. Multiple emboli were found in branches of the inferior mesenteric artery. In addition, a healed duodenal ulcer, bilateral nephrolithiasis, and chronic pyelonephritis were found. Case 10 revealed to the pathologist a left calculus pyonephrosis, cholelithiasis, choledocholithiasis, and hepatic lithiasis. Cirrhosis of the liver was an additional lesion in Case 3.

The associated renal lesions are worthy of separate consideration since this series shows, in striking fashion, the difference between the active and bacteria-free cases, as pointed out by Libman,[40] and Baehr and Lande.[41] Four of the six cases in Group A showed focal embolic glomerulonephritis without any clinical evidence of renal insufficiency, while two of the five bacteria-free cases showed chronic diffuse glomerulonephritis at post-mortem examination, associated with clinical signs of marked renal insufficiency and with increased urea nitrogen in the blood. Another case in this group disclosed renal insufficiency due to massive focal embolic glomerulonephritis.

Gross infarcts of the kidneys were noted in Cases 4, 11, 15, and 17. In the last case, the left adrenal gland was also involved by infarct. Among other embolic phenomena are noted multiple embolic abscesses of the myocardium, kidneys, spleen, and intestines in Case 1, mycotic aneurysm at base of aorta, multiple mycotic aneurysms of the superior mesenteric and right iliac arteries

in Case 2; and cerebral embolism in Case 16. In general, fewer infarctions were found in the bacteria-free group of cases.

BACTERIOLOGY

Of the nine cases classified as active (Group A), *Streptococcus viridans* was recovered from the blood stream in seven, *Enterococcus* and *Hemophilus parainfluenzae* in one each. Of the five bacteria-free cases (Group B, 1), blood cultures were not taken in two and in the others were repeatedly sterile. Of the clinically obscure cases (Group B, 2), blood cultures were not performed in three, and in the remaining case, six cultures were taken, of which only the fifth revealed *Str. viridans,* its source being erroneously ascribed to an acutely inflamed parotid gland.

In none of these cases was a mixed infection found, although in two of our series of acute bacterial endocarditis cases, two organisms were isolated from the blood stream. *Enterococcus* and *Staphylococcus albus* were associated in one patient; *Pneumococcus* and *Streptococcus hemolyticus* in the other. Libman and Friedberg[22] mention two types of mixed infection in subacute bacterial endocarditis. "The most common combination is an endocarditis due to an hemolytic streptococci with a secondary pneumococcus bacteremia, usually secondary to lobar pneumonia. We have observed also a secondary implantation of *Staphylococcus aureus* on valvular vegetations due to non-hemolytic streptococci." Orgain and Poston[42] have reported six patients with bacterial endocarditis from whose blood they repeatedly cultured two or more distinct species of bacteria. There was little in the history, physical examination, laboratory data, and clinical course of their cases to suggest a mixed infection. They emphasize that recognition of a mixed infection is of fundamental importance in sulfonamide therapy, since the drug may affect one organism and not the other.

The occurrence of *H. parainfluenzae* as the cause of subacute bacterial endocarditis is well known. Rose,[43] in a recent communication, has pointed out the bacteriologic differentiation between *H. influenzae* and *H parainfluenzae,* emphasizing the great rarity of the former in endocarditis. He contributes an authentic case of *H. influenzae,* Type A., endocarditis.

The portal of entry of the infection in subacute bacterial endocarditis is nearly always obscure, although the upper respiratory tract and the teeth are frequently implicated on the basis of clinical study. In this series of old people the associated and unrelated pathologic lesions may be of importance, such as the bilateral nephrolithiasis in Case 2, the healed (?) osteomyelitis of the jaw in Case 5, and the left pyonephrosis and biliary lithiasis in Case 10. That there is a specific lowering of resistance to bacterial infection attributable to the changes of senescence, can only be inferred from the occurrence of the valvular infection late in the life of individuals who had undoubtedly carried rheumatic valvular lesions throughout a large part of their lives. Other explanations of equal validity are possible.

CLINICAL FEATURES

Table IV gives the age and sex distribution of the eighteen cases. The male cases predominate over the female, and, while these figures can have but little significance, it will be recalled that in series of younger patients the disease also seems more prevalent among men. Thirteen of the cases occur in the first half of the seventh decade of life, one in the second half, three in the first half of the eighth decade, and one in the second half of the ninth. These figures

TABLE IV. DISTRIBUTION OF CASES ACCORDING TO AGE AND SEX

AGE (YRS.)	MALE	FEMALE
60 to 64	7	6
65 to 69	1	-
70 to 74	2	1
75 to 79	-	-
80 to 84	-	-
85 to 89	1	-
Total	11	7

may be compared with those cited from other sources in our review of the literature.

The eighteen cases herewith reported have been separated into three groups on the basis of the clinical pictures presented and the difficulties each group places in the way of correct diagnosis. In the first group of nine cases the clinical diagnosis presented only moderate difficulty and was confirmed in the six cases which came to autopsy. In the second group of five cases the correct diagnosis was made clinically in only two, and of the third group of four cases none was interpreted correctly. Of the total eighteen cases the clinical diagnosis was made correctly in eleven, or 61 per cent. In the Bayles and Lewis series of twenty-eight individuals over 40 years of age, one-half received the correct diagnosis ante mortem.

THE TYPICAL, BUT OFTEN MODIFIED, CLINICAL PICTURE (GROUP A)

Libman and Friedberg[22] list the four following features in combination as leading to the diagnosis of subacute bacterial endocarditis: "(a) a valvular defect or a congenital lesion, (b) a febrile course, (c) embolic phenomena, and (d) a positive blood culture." These criteria are amply satisfied by the cases in Group A, but certain features will be pointed out which tend to modify the typical clinical picture and to make the diagnosis difficult at times. Prerequisite to diagnostic accuracy is the knowledge that subacute bacterial endocarditis may occur in the aged, and the clinician must fit his observations into a line of thought that suggests the value of taking a blood culture. In my first case, mentioned briefly in the introduction, a whole month passed before the value of this procedure occurred to me. In old people cardiac murmurs are common, and are customarily dismissed as "arteriosclerotic," although careful study is often required to establish their true cause and significance. Fever in old persons is not uncommonly of low-grade intensity, and, if not overlooked entirely, is apt to be explained away as due to a "patch of bronchopneumonia" or to an infection of the urinary tract.

Study of the clinical records of the nine cases in Group A shows that all had heart murmurs, although some were incorrectly interpreted, as in Case 9. All but one had red blood cells in the urine, many showed albuminuria, but none had evidence of renal insufficiency. Petechiae were abundant in two persons, rare in three persons, and not observed in four. Fever was regularly present in these patients, even in the man 87 years of age (Case 3). Clubbing of the fingers was noted in two cases. The spleen was palpable in five cases, the liver in four. Anemia was present in only four of these cases. All had positive blood cultures, seven showing *Str. viridans*, and one each, *Enterococcus* and *H. parainfluenzae*, but positive cultures were not always obtained on the first attempt.

In retrospect one finds that each of these cases conformed to Libman's four diagnostic criteria. Study of typical case histories will indicate, however, that

the correct diagnosis was not always directly arrived at, partly because of misplaced clinical emphasis, and partly because the bedside observations did not at once fit into a diagnostic whole. The following case history is noteworthy because of the advanced age of the patient, the minimal underlying arteriosclerotic changes in the valves, the comparative well-being of the patient for many weeks, and the large numbers of bacteria in the blood stream at all times with minimal clinical manifestations.

CASE 3.—This 87-year-old physician had enjoyed good health except for prostatism. Five weeks before admission, malaise, chilly sensations, and fever were noted. Later, shaking chills occurred on several occasions. On examination he was found to be a thin, well-preserved, elderly man with a temperature of 102° F.; moderate general arteriosclerosis; heart, not enlarged, with a harsh systolic murmur at the apex; and liver enlarged 2 fingerbreadths below the costal margin. The hemoglobin was 85 per cent, and the white blood cell count was 14,000 with 80 per cent polymorphonuclears. The urine contained albumin but no red blood cells. An electrocardiogram showed left axis deviation, small Q_1, and slurred QRS. Repeated blood cultures showed *Str. viridans* in all flasks. Only rarely were petechiae found.

Sulfapyridine had no effect on the bacteriemia, and other methods of therapy, such as hyperthermia, seemed too strenuous to attempt. The mild course of this infection in the early stages was very striking. The patient was frequently able to be out of bed, particularly in the morning, and outwardly looked remarkably well. He died four and one-half months after onset.

On post-mortem examination (Montefiore Hospital) the following findings were established: mild arteriosclerosis of mitral and aortic valves, with superimposed bacterial endocarditis; infarctions of spleen and kidneys; focal embolic glomerulonephritis; arteriosclerosis of coronary arteries, general arteriosclerosis; chronic cholecystitis and cholelithiasis; benign hypertrophy of prostate.

The confusion caused by presenting symptoms pointing to either a suppurative or neoplastic lung lesion is well illustrated in an elderly man suffering from syphilitic aortitis. Notable in this case were the absence of splenic enlargement and of embolic phenomena except red blood cells in the urine, the well-marked euphoria (*Spes endocarditica* of Horder), and the progressive change in the patient's facies to a well-defined *café-au-lait* coloration.

CASE 6.—For six weeks this 64-year-old butcher suffered from cough, productive of one cupful of malodorous sputum daily, and had lost 22 pounds in four months. There was no history of syphilis or rheumatic fever. On examination he was pale, his pupils were irregular, but reacted to light; and his heart showed a diastolic murmur audible at left border of sternum. Blood pressure was 150/60. Moderate clubbing of the fingers was noted. The hemoglobin was 60 per cent, and the white blood cell count was 16,000 with 76 per cent polymorphonuclears. The Wassermann and Kahn reactions were strongly positive. Roentgen examination of the chest showed an infiltration near the right border of the heart. Lipiodol demonstrated a cylindrical dilatation of right lower lobe bronchus.

On admission, the general diagnostic opinion favored either a suppurative bronchopneumonia or a pulmonary neoplasm. Two bronchoscopic examinations failed to give confirmation to these views, and also failed to account for the daily rise in temperature up to 102° F. at night. Only then were all the facts correlated; namely the fever, anemia, microscopic hematuria, aortic insufficiency, and early clubbing of the fingers. Blood culture, when finally taken, revealed a *Str. viridans* bacteremia. The patient was discharged to the care of his own physician nine weeks after admission. He died, at home, two weeks later. Necropsy was not performed.

THE BACTERIA-FREE CASES (GROUP B, 1)

To Libman[40] we owe the description of the "cases of subacute bacterial endocarditis that have spontaneously become bacteria-free." He has emphasized that the clinical picture of this phase of the disease is due to damage to the kidneys and the blood-forming organs during the bacterial stage and to embolism

due to the fibrous and calcified vegetations resulting from the healing process. For a fatal case to be considered in the bacteria-free stage, the vegetations must be shown by spreads and sections to contain no bacteria. The mere absence of bacteria from the blood stream, even after repeated attempts at culture, is not enough to show that the heart valves are free of infection, since this may also occur from time to time in the active cases. In establishing the clinical diagnosis, Libman emphasized the following features in association with chronic valvular disease: renal insufficiency, severe progressive anemia, emboli, striking splenomegaly, and brown pigmentation of the face. Keefer[44] has stressed the fact that 20 to 25 per cent of all cases, as proved by post-mortem examination, belong in the group without bacteriemia. He distinguished five classes: (a) patients with right-sided valvular disease, multiple pulmonary infarcts, and jaundice; (b) patients with renal insufficiency; (c) patients with heart failure; (d) patients with splenomegaly and anemia; and (e) patients with hemiplegia. He considers renal insufficiency as the most important clinical difference between these cases and those with positive blood cultures.

Five cases in this series have been classified as belonging in the bacteria-free group. Two of these (Cases 11 and 14) were diagnosed correctly before death. In Case 10 the clinical picture was dominated by long-standing rheumatic valvular disease, cardiac failure, and renal insufficiency. In Case 12 renal insufficiency again obscured the real significance of the symptoms. In Case 13 cardiac failure combined with hepatic cirrhosis seemed an adequate explanation of the clinical findings.

Regarding the details of the clinical picture we note that two patients were males, three were females, and the age range was from 60 to 74 years. Fever was present in one case, and in only one was a change in facial color noted. Clubbing of the fingers was present in two cases, and petechiae were observed in two cases. Heart failure was present in three cases, but arrhythmia occurred in only one; the liver and spleen were enlarged and palpable in all five cases. Anemia was present in three cases; renal insufficiency in four. Blood cultures were taken in three cases and showed no growth, even on repeated attempts. In the other two cases blood cultures were not done because there seemed to be no clinical indications.

At necropsy, bacteria were not present in the valve crushings. In two cases the vegetations contained deposits of calcium. The occurrence of chronic glomerulonephritis has already been emphasized in the section devoted to pathology. The following case histories will clarify the problems posed by the bacteria-free group. Case 11 presents the classical features of the bacteria-free stage, as described by Libman, especially the death in uremia, associated with congestive heart failure and auricular fibrillation:

For many years this 64-year-old woman had suffered from rheumatic heart disease. She was re-admitted because of increasing weakness, epistaxes, nausea, and emesis. When seen some weeks before, fixation of specific gravity of urine and moderate nitrogen retention in the blood had been noted. On admission examination marked asthenia and muscular twitchings of the upper extremities were noted; linear hemorrhages were found in the fundus oculi; dullness was present at both lung bases with râles at the right base; the heart was enlarged to the left; the sounds were of fair quality; a long blowing systolic murmur was heard over the precordium, maximal at base and propagated toward vessels of the neck, with a thrill at the base; the rhythm was totally irregular. The blood pressure was 130/60. The spleen was enlarged to the umbilicus, and the liver edge was felt 4 cm. below the costal margin. No petechiae were observed. The hemoglobin was 42 per cent; the red blood cell count was 2,500,000; and the white blood cell count was 3,500, with a normal differential count. Unfortunately the patient died within twenty-four hours before blood for urea nitrogen de-

termination could be drawn. Diagnostic discussion leaned to bacteria-free subacute bacterial endocarditis, based on the cardiac findings, the anemia, the splenomegaly, and the symptoms of uremia.

Post-mortem examination disclosed: healing subacute bacterial endocarditis with calcification of vegetations, involving aortic and mitral valves; chronic rheumatic valvular disease, tricuspid, mitral, and aortic valves; focal embolic glomerulonephritis and diffuse glomerulonephritis; marked splenomegaly.

In Case 12 the clinical picture of endocarditis is obscured by the renal insufficiency. The necropsy findings lead one to conclude that the blood culture, had it been done, would have proved sterile.

History was elicited with difficulty from this 74-year-old man. In past year he had suffered from a moderate cough, dyspnea on exertion, and urinary urgency and frequency; just before admission hematuria and melena were observed. On examination he was found febrile, cyanotic, dyspneic, with heart sounds distant, and an aortic diastolic murmur audible. The blood pressure was 126/150. There was congestion at both lung bases; enlarged liver, spleen, and prostate; and general peripheral sclerosis. The hemoglobin was 60 per cent, and the white blood cell count was 8,000, with 60 per cent polymorphonuclears. Urine contained large amounts of albumin, occasional hyaline and granular casts, and frequent red and white blood cells. Urea nitrogen was 37 mg. per cent. Electrocardiogram showed regular sinus rhythm, frequent ventricular extrasystoles, QRS moderately low, and P waves low. Urea nitrogen rose gradually to 83 mg., and the patient died ten days after admission, in uremia. Blood culture was not done, as the true diagnosis was at no time suspected.

Post-mortem examination showed the following: subacute bacterial endocarditis (bacteria-free) of the aortic valve with perforation of the right anterior cusp; chronic rheumatic valvular disease, mitral insufficiency; aortic stenosis and insufficiency; infarct of the spleen; focal embolic glomerulonephritis and chronic diffuse glomerulonephritis; general arteriosclerosis; coronary arteriosclerosis with narrowing; and fibroadenoma of the prostate.

THE COMPLETELY OBSCURE CASES (GROUP B, 2)

The four cases, which have been included in Group B, 2 as completely obscure, clinically, exemplify vividly the varied ways in which the diagnosis may be missed. In the bacteria-free cases renal insufficiency proved the greatest stumbling block. Here, in order, we find congestive heart failure due to rheumatic and thyrotoxic heart disease, hemiplegia of unsuspected embolic origin (Case 16), chronic valvular disease in association with acute parotitis (Case 17), and a mistaken diagnosis of gastrointestinal malignancy (Case 18), leading the clinician astray. Of the four cases, three are in the active phase and the fourth is in the bacteria-free stage, although no blood cultures were taken in any of them.

Libman and Friedberg state that the fatigability, weakness, sweating weight loss, nervous symptoms, and the elevated basal metabolic rate of subacute endocarditis may simulate Graves' disease, but they also warn that a patient with Graves' disease may develop subacute endocarditis. Hoff[19] has reported a man, 55 years of age, suffering from subacute bacterial endocarditis with splenomegaly and anemia. Within one year of death, his disease had been diagnosed as toxic goiter. Thyroidectomy was performed a year previously, and again, four months before death. He had been given two courses of deep roentgen therapy, the last one immediately before admission to the hospital.

In Case 15 we find a woman, aged 70 years, who had a symptomless goiter for twenty years. For one year year loss of weight, easy fatigue, polyphagia, elevated basal metabolic rate, dyspnea, orthopnea, and edema of the legs had been noted. The clinical picture was that of congestive heart failure due to Graves' disease. At post-mortem examination subacute bacterial endocarditis of the tricuspid, mitral, and aortic valves was a surprising finding, as was the

disclosure of chronic rheumatic valvular disease of the tricuspid, mitral, and aortic valves. Focal embolic glomerulonephritis was present. In this patient the endocarditis is believed to be secondary to both rheumatic and thyrotoxic heart disease.

Case 16, which follows, served originally to crystallize the writer's interest in this phase of the problem, since the hemiplegia was thought by all to be of local vascular origin. No one for a moment considered that it might be embolic. The fever was likewise "explained away," and the enlarged spleen was not identified although easily palpable.

For thirteen years, this 62-year-old woman had hypertension with occasional vertigo and syncope. On the morning of admission to the Mt. Sinai Hospital, she was found with complete right hemiplegia, unable to speak. Blood pressure at home was 208/108. These findings were confirmed in the hospital, where the heart rate was regular but rapid; a systolic murmur at the apex and base was noted. A mass in the left upper quadrant was felt, and was described as large, hard, irregular, and immovable. The hemoglobin was 68 per cent; the red blood cell count was 4,380,000; and the white blood cell count was 21,000 with 81 per cent polymorphonuclears. The urine contained albumin, a few hyaline and granular casts, and a moderate amount of white blood cells.

The patient ran an irregularly febrile course during her stay in the hospital with temperature ranging between 99° and 103° F. It was assumed that the fever was due either to the cerebral vascular accident or some intra-abdominal inflammatory disease, as suggested by the left upper quadrant mass. She lost ground gradually and died eight days after admission.

Post-mortem examination disclosed subacute bacterial endocarditis of the anterior leaflet of the mitral valve; multiple emboli to the spleen and kidney; acute fibrinous pericarditis; old occlusion of the right coronary artery; and aneurysm of the left ventricle with acute myomalacia and myocardial fibrosis.

The involvement of the central nervous system in endocarditis has been discussed by Kernohan, Woltman, and Barnes.[45] These authors stress the occurrence of embolic lesions leading to hemiplegia, Jacksonian attacks, hemianopsia, aphasia, brain abscess, and meningitis. Toone[46] has emphasized that the basic brain pathology in endocarditis is an embolic meningo-encephalitis, and that these brain lesions frequently produce the outstanding clinical features of the syndrome.

In Case 17 every effort was made to establish the presence of a bacteriemia, but when one of six attempts showed *Str. viridans* it was attributed to an acute parotitis. In view of the evidences of healing found in vegetations at autopsy this interpretation may have been correct. The long period of hospital observation, eight weeks, is noteworthy.

Five months previously, this 62-year-old man suffered myocardial infarction necessitating two months' rest in bed. For three months before admission he had noted insomnia, asthenia, dyspnea on exertion, pallor, and a 20 pound loss in weight. During this period his physician observed development of systolic and diastolic murmurs audible at the base of the heart. At admission examination he was found to have one conjunctival petechia, cardiac enlargement, systolic and diastolic murmurs at both apex and base; blood pressure, 134/65; liver enlarged; spleen, firm edge, just palpable; clubbing of fingers. The hemoglobin was 52 per cent; red blood cell count was 4,000,000; and the white blood cell count was 5,200; with 60 per cent polymorphonuclears.

During the patient's first three weeks in the hospital, his fever ranged between normal and 101° F. Urine sediment showed red blood cells. Blood urea nitrogen rose from 25 to 37 mg. per cent. After six weeks in the hospital, acute left parotitis developed, responded to radiotherapy, and drained through the duct. Culture of pus yielded *Staph. albus, Staph. aureus, Enterococcus,* and *Str. hemolyticus.* In all, six blood cultures were made. All were negative except the fifth, from which *Str. viridans* was cultured in one flask. As this was

found at onset of parotitis, its origin from the heart valves was doubted. The electrocardiogram originally showed left bundle branch block with left ventricular hypertrophy and marked myocardial damage, but no progression was seen in subsequent tracings. The patient became abruptly worse during his eighth week in the hospital; his urea nitrogen mounted to 70 mg. per cent; he vomited repeatedly, became dehydrated, and died. Post-mortem examination disclosed subacute bacterial endocarditis (healing) of the mitral and aortic valve; aneurysm of the mitral valve, two dissecting aneurysms of the aortic valve; splenic, renal, and left adrenal infarctions; rheumatic heart disease, mitral and aortic insufficiency and stenosis; bicuspid aortic valve, etiology (?); old occlusion, incomplete, of anterior descending branch of the left coronary artery; aneurysm of the apex of the left ventricle and inferior anterior one-third of septum; arteriosclerosis of the aorta, coronary arteries, and pulmonary arteries; chronic cholelithiasis and cholecystitis; fibro-adenoma of the prostate.

In Case 18, fever, anemia, heart disease, and microscopic hematuria were shown clinically, which, viewed in retrospect, should have led to clinical suspicion of the true state of affairs. Weight loss and constipation prompted the search for a malignant tumor of the gastrointestinal tract.

Two years previously, this 62-year-old man first learned that he was suffering from hypertension and cardiac hypertrophy. For the preceding few months increasing weakness and weight loss were noted, with occasional nocturnal dyspnea. He appeared pale and chronically ill; the heart was markedly enlarged with an apical systolic murmur and snapping first sound. The blood pressure was 178/100. The hemoglobin was 62 per cent; the white blood cell count was 15,750, with 57 per cent segmented polynuclears, 32 per cent nonsegmented, 4 per cent lymphocytes, and 7 per cent monocytes. The urine showed a faint trace of albumin and a moderate number of red cells. The electrocardiogram showed slight slurring of the QRS complex.

Because of weight loss, constipation, and rapid sedimentation rate, a gastrointestinal malignancy was at first suspected. Sigmoidoscopy and barium enema showed no abnormality. Renal studies were planned because of hematuria, but whole blood transfusion was considered a necessary preliminary. The patient died in pulmonary edema thirty minutes after the transfusion.

Post-mortem examination surprisingly disclosed: subacute bacterial endocarditis of the mitral and aortic valves and the wall of the left auricle; chronic rheumatic valvular disease, mitral and aortic valves, with calcification of mitral chordae tendineae; acute splenic tumor; hypertrophy of both ventricles; pulmonary edema and emphysema; and arteriosclerosis of the kidneys. Crushings of vegetations showed gram-positive cocci abundantly.

The difficulties in diagnosis due to the latency of the endocarditis have been strongly emphasized by Musser.[47] He cites a man, 50 years of age, who died as the result of congestive heart failure and bilateral brachial emboli. The post-mortem finding of subacute bacterial endocarditis was entirely unsuspected. A recent case record[48] from the Massachusetts General Hospital deals with a woman, 54 years of age, who showed, on admission, arteriosclerosis, diastolic hypertension (184/110) and hepatomegaly. She was operated upon to relieve uterine prolapse. Vaginal hysterectomy and perineorrhaphy under gas-ether anesthesia were performed. The operation lasted three hours, and toward its close a sharp drop in blood pressure was noted. The patient died twenty-four hours later. The clinical diagnosis was a cerebral vascular accident. At post-mortem examination an embolus was found in the left middle cerebral artery, but its source was subacute bacterial endocarditis of the mitral valve superimposed on chronic rheumatic valvular disease, mitral stenosis.

DIFFERENTIAL DIAGNOSIS

The preceding cases indicate the broad range of differential diagnosis required in establishing the presence of subacute bacterial endocarditis in the aged. Heart disease due to congenital lesions, rheumatic fever, or syphilis may be present in old people, and together with the commonly found triad of

coronary artery sclerosis, coronary artery thrombosis, and myocardial infarction, serve as the background for an endocarditis. Neurological complications, as well as renal insufficiency and signs such as weight loss and anemia, pointing to the presence of malignant tumors, may mask the disease. While the finding of a positive blood culture would seem to clarify diagnostic problems, there are occasions when the opposite occurs. Herrmann[49] has reported a series of such cases in younger individuals.

In the following case the presence of a heart murmur, petechiae, and a positive blood culture led to an incorrect clinical diagnosis of endocarditis.

A man, aged 55 years, who had suffered from diabetes for over twenty years, developed a gangrenous cellulitis of the right foot following an injury. Amputation was finally performed, although just before operation the patient suffered an attack of myocardial infarction, proved by electrocardiogram. Following operation he did well; the stump healed without sign of infection; he became afebrile and was allowed out of bed after one week. He was discharged and about to leave the hospital when, on the twenty-second day after amputation, his temperature rose suddenly to 104° F. The following day the temperature was 103.2° F. The twenty-third day it became normal and remained so for three days. On the twenty-ninth day postoperatively he had a chill which recurred on the thirtieth, thirty-third, and thirty-fifth postoperative days. Blood culture contained *Str. viridans*. Examination of the stump proved normal, but the femoral vein was ligated as a precaution. Sulfonamide therapy did not affect the blood stream infection. Petechiae and a heart murmur were now detected. The patient died ten weeks after admission as the result, it was thought, of subacute bacterial endocarditis. At post-mortem examination, the findings were: thrombosis of the left renal artery with suppurating infarct of the right kidney; severe coronary sclerosis with narrowing and recent thrombosis of the left circumflex branch; myomalacia of the posterior wall of the left ventricle with abscess in the papillary muscle.

TREATMENT

Excellent reviews of the results of treatment of subacute bacterial endocarditis prior to the introduction of the penicillin-heparin method have been contributed by Smith, Sauls, and Stone,[50] Lichtman,[51] and Eggleston.[52] In January, 1944, the startling report of the work of Loewe, Rosenblatt, Greene, and Russell[7] appeared, giving the details of the administration of heparin and penicillin and the case histories of seven consecutive patients who were successfully treated. Included among their more recent and unpublished successful cases are at least two individuals over 60 years of age.[53] It seems likely, therefore, that the improved therapeutic prospect will include older patients as well as the younger ones. The complete lack of toxicity of penicillin makes it an ideal drug for use in aged individuals.

Of nine cases reported here, and included in the active group with bacteriemia, six were treated intensively by the older methods. Case 3 was given sulfapyridine without benefit. Case 4, in which the causative organism was *H. parainfluenzae*, was under observation with intermittent administration of sulfadiazine for over one year. He seemed at times to be definitely benefited by the sulfonamide therapy, and it probably prolonged his life. In Case 5 sulfapyridine, sulfathiazole, and hyperthermia were without effect. In Case 7 sulfapyridine and sulfathiazole produced a brief temporary sterilization of the blood stream. In Case 8, the patient received sulfadiazine and seven hyperthermia treatments without any improvement. In Case 9 the patient was given sulfadiazine intravenously without effect on the clinical course.

SUMMARY

The literature relating to the incidence of bacterial endocarditis among the aged has been reviewed. Eighteen cases of this disease in persons ranging in

age from 60 to 87 years are analyzed, emphasizing the high incidence of rheumatic valvular lesions as the basis for the endocarditis, with the occurrence in this role less frequently and in the order named, of arteriosclerotic, syphilitic, congenital, and thyrotoxic heart disease.

By classifying the cases into two large groups according to the diagnostic problems presented, it has been possible to show that approximately one-half of the cases exhibit a typical, though often modified, clinical picture, and that the second group of more difficult cases may be further subdivided. In the first subdivision are placed the bacteria-free cases, characterized predominantly by heart failure, splenomegaly, anemia, and renal insufficiency. Into the second subdivision are placed the cases which completely elude precise diagnosis, due to the masking of the endocarditis by envolvement of the central nervous system and by a bewildering variety of other clinical findings which tend to distort diagnostic emphasis.

The multiplicity, chronicity, and duplicity of disease in the aged cannot be stressed too often. These cases of endocarditis show in striking fashion how this disease forms the closing incident of a long life during which time many maladies have been acquired and either overcome or endured. The writer believes that the difficulties of accurate differential diagnosis of disease in the aged, as exemplified in these case presentations, offer a stimulating challenge to the keen clinician. Diagnostic success holds out the hope of possible therapeutic achievement by using the newer methods of combating infections.

This study of subacute bacterial endocarditis in the aged demonstrates anew the inestimable value of clinical and pathologic correlations, along the lines laid down by Morgagni nearly two hundred years ago. In this modern day, it would hardly seem necessary to belabor the point, but for real progress in the diagnosis of disease in the aged, more old people must be studied by the pathologist as well as by the clinician. The general hospitals have a large responsibility as regards the acute medical and surgical problems of the aged, but vast fields of investigative endeavor lie open for the progressive homes for the aged where the clinicial material is largely made up of the chronic, insidious, and slowly progressive disorders of old age, and where the residents are under observation over long periods of time.

CONCLUSIONS

1. At the present time subacute bacterial endocarditis occurs in the aged more frequently than is generally realized. With the increase in the number of old people in the population, an increased incidence of this disease may be expected in the higher age groups.

2. Clinical recognition of subacute bacterial endocarditis depends upon the physician's constant effort to achieve diagnostic accuracy in the aged by utilizing for them the same careful observation and the same methods of precision commonly employed for the young.

3. The chief obstacle to diagnostic exactitude lies in the multiplicity of the pathologic processes in old people and in the difficulty of determining the relationship of these processes to the total clinical picture. In spite of close observation and study there will still remain a group of cases in which the subacute bacterial endocarditis will first be disclosed on the autopsy table. Additional clinical and pathologic investigations are needed to keep down the number of these post-mortem surprises.

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THE ELECTROCARDIOGRAM AND CARDIAC STATE IN ACTIVE SICKLE-CELL ANEMIA

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THIRTY years have passed since Herrick described the first cases of drepanocytic anemia.[1] During this time much has been written about this interesting disease. Approximately 145 articles, containing 388 reports of active cases with anemia, have appeared.[2] Only four of these articles, however, deal with the cardiac aspect of this condition.[3-6] There has been no detailed analysis of the electrocardiographic changes in this disease, although many of the case reports have included isolated electrocardiograms. Since an adequate number of patients with active sickle-cell anemia who have been repeatedly examined carefully cardiologically during a period of three years were available for further investigation, it was considered advisable to study the cardiac state and the electrocardiogram in this disease.

At first glance it would appear that this type of cardiac disease affects only a few members of the Negro race. This is not true in the South. During a single year, 1941 to 1942, at Charity Hospital in New Orleans, forty patients with this disease were admitted to the wards. The great majority of these patients had heart disease. It is to be noted that, among the Negro patients at Charity Hospital, heart disease in sickle-cell anemia is encountered more frequently than heart disease due to beriberi, myxedema, periarteritis nodosa, trauma, or pernicious anemia. The apparent infrequency with which heart disease in sickle-cell anemia is encountered seems to be due to the fact that this condition is often unrecognized. It is frequently confused with rheumatic heart disease, congenital heart disease, or bacterial endocarditis.

The problem of heart disease in sickle-cell anemia is not confined entirely to persons with Negroid characteristics, for it has been observed in patients who are "socially" white, and in such cases the diagnosis is rendered more difficult. Whether or not sickle-cell anemia occurs among persons who are free from Negro blood is difficult to ascertain. Nevertheless, neither color nor racial features rule out the possibility of sickle-cell anemia heart disease.

Heart disease in sickle-cell anemia is one of the few types of heart disease which is hereditary. Once the diagnosis of sickle-cell anemia is established in a family, heart disease should be considered in all other members of the group.

It is because of the paucity of information dealing with heart disease in sickle-cell anemia, the frequency of this condition in localities where there is a substantial Negro population, and the frequency with which this type of heart disease is overlooked that the cardiac state and the electrocardiographic picture are discussed.

METHODS AND MATERIALS

This study includes only patients with active sickle-cell anemia. Patients with any of the following complications were excluded: acquired or congenital syphilis, a blood pressure or more than 140 mm. Hg, systolic, or 90, diastolic, an erythrocyte count greater than 3,500,000, a history of diphtheria or any other severe infection, or any discernible cause for

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heart disease other than sickle-cell anemia. Patients who were receiving digitalis, quinidine, morphine, insulin, xanthine derivatives, diuretics, or salicylates were not included.

All patients had a thorough cardiac survey, including electrocardiographic, fluoroscopic, and teleroentgenographic examination, as well as a complete hematologic investigation. The diagnostic parameters, $\triangle_1$ and $\triangle_2$, were ascertained routinely in most of the cases.[7]

The electrocardiograms were recorded by means of the Hindle galvanometer.* The standard and precordial leads were analyzed in the usual way for the amplitude and duration of the respective complexes. All electrocardiograms were taken with the patient in the supine position, and all records were properly standardized.

Of eighty-five patients with sickle-cell anemia, twenty-five were suitable for study. The cardiac state of these patients was studied from the clinical and electrocardiographic points of view. The average age was 13 years. The youngest was 1, and the oldest, 27 years. Forty per cent of the patients were females. In addition, the pathologic changes were studied in nine other post-mortem subjects.

The normal values for the electrocardiograms used for comparison in these studies are taken from the work of Ashman and his collaborators.[8, 9] All normal values given are for adults unless stated otherwise.

RESULTS

I. *Clinical.*—The clinical cardiac data are shown in Tables I, II, and III. The blood pressures averaged 112/71, and varied between 94/50 and 130/80.

TABLE I. CLINICAL AND ELECTROCARDIOGRAPHIC OBSERVATIONS ON TWENTY-FIVE PATIENTS WITH SICKLE-CELL ANEMIA

PATIENT	AGE (YR.)	SEX	RBC (MILLION)	PULMONARY CONUS	RV	LV	CT RATIO (%)	CARDIAC RATE (BEATS/MIN.)	ANATOMIC AXIS (DEGREES+)	AXIS DEVIATION OF THE QRS (AREAS, DEGREES+)
1	18	M	2.8	0	+++	+++	59.1	80	25	37
2	6	M	3.2					114		40
3	2	M	3.0	+++	+++	++++	62.0	101	22	47
*4	22	M	2.8	++	++	+++		84		64
5	10	M	2.7	+	++	++	55.0	90	25	6
†6	12	F	2.9					60		60
‡7	10	M	3.5	0	+++	0	50.0	75	25	59
8	10	M	2.3	0	++++	++++		101	21	34
9	15	M	2.8	+++	0	+++	53.3	125	30	70
10	21	F		+++	+++	+++		76		30
11	7	M	1.4	+++	+++	++++		90		44
12	21	F	2.3	++	++++	++	56.6	83	45	61
13	10	F	1.8	+	++	+++	45.5	86	21	47
14	25	F	1.5				65.0	70		50
15	10	F		+	+++	++	60.0	110		72
§16	6	F	1.8	+++	+++	+++	60.8	86		125
17	6	F		++	+++	++	57.0	94	22	40
18	4	M	2.3	+	++	++		90		54
19	27	M	1.7	0	0	0		57		47
20	1	M	3.5	++	+++	+++		125	42	58
21	15	M	1.0	+	+++	+++		88		0
‖22	14	M	2.7	0	0	++		101		53
23	26	F	2.0	0	++	++		80	18	40
24	16	M	1.9	++++	++++	++++	65.0	80	30	50
25	13	F	2.0	++	++	++++	54.0	104	30	51
Mean	13.0		2.4				57.2	90	27.3	49.5
Maximum	27.0		3.5				65.0	125	45.0	125.0
Minimum	1.0		1.0				45.5	60	18.0	0.0

Abbreviations: RV = right ventricle.
LV = left ventricle.
CT = cardiothoracic.

*Q-T interval greater than normal by 0.05 second.
†P-R interval greater than normal by 0.01 second.
‡P-R interval greater than normal by 0.02 second.
§Deviation of QRS axis +125 degrees. Clinically, pulmonary infarction.
‖P-R greater than normal by 0.02 second, T_1 low.

*Cambridge Instrument Company, Ossining, New York.

The average erythrocyte count was 2,400,000, and the extremes were 1,000,000 and 3,500,000 cells per cubic millimeter. The diagnostic parameters averaged 49 mm. per hour, and varied between 32 and 72 millimeters.

Cardiac murmurs were present in 95 per cent of the group (Table II). Dyspnea on exertion and a cardiothoracic ratio of 50 per cent or greater were present in 85 per cent of the cases. Hepatomegaly was present in 52 per cent, edema of the legs in 24 per cent, and precordial pain in 15 per cent. There was some degree of cardiac enlargement in 95 per cent of the cases as ascertained fluoroscopically. The left ventricle was enlarged in 91 per cent of the cases, the right ventricle in 86 per cent, and the pulmonary conus in 73 per cent.

TABLE II. CARDIAC SIGNS AND SYMPTOMS IN TWENTY-FIVE CASES OF SICKLE-CELL ANEMIA

SIGN OR SYMPTOM	FREQUENCY (PER CENT)
Temperature of 100° or over	95
Cardiac enlargement	
Left ventricular	91
Right ventricular	86
Pulmonary conus	73
Cardiac murmurs	95
Dyspnea on exertion	85
Cardiothoracic ratio 50 per cent or greater	85
Hepatomegaly	52
Leg edema	24
Precordial pain	15

TABLE III. TYPES OF CARDIAC MURMURS IN TWENTY-FIVE CASES OF SICKLE-CELL ANEMIA

MURMUR	FREQUENCY (PER CENT)
Mitral systolic	48
Pulmonary systolic	19
Aortic systolic	14
Aortic systolic and diastolic	5
Pulmonary systolic and diastolic	5
Mitral systolic and diastolic	5
Thrill (mitral)	5

The types of cardiac murmurs are summarized in Table III. In general, the murmurs were loud, and were a prominent physical sign. Mitral systolic murmurs occurred in 48 per cent of the cases. These murmurs were frequently transmitted over the entire precordium and posterior aspect of the thorax. In 5 per cent the mitral systolic murmur was associated with a presystolic rumble. Pulmonary systolic murmurs occurred in 19 per cent of the cases. In 5 per cent there was a systolic and a diastolic pulmonary murmur. Accentuation of the pulmonary second sound was frequently present. An aortic systolic murmur occurred in 14 per cent of the cases, and, in 5 per cent, there were an aortic systolic murmur and an early, soft, blowing, aortic diastolic murmur. A mitral thrill was present in 5 per cent of the cases.

The anatomic axis of the ventricles (obtained from teleroentgenograms), as measured through the main muscle mass of the ventricles, averaged 27.3 degrees and varied between 45 and 18 degrees (Table I).

II. *Pathologic Data.*—Nine autopsied patients (Table IV) were studied from the standpoint of cardiovascular changes. Two of the patients died after surgical procedures, three died after childbirth, three died of congestive heart failure, and one died after a blood transfusion. The average age at death was 24 years, and the extremes were 10 and 35.

The mean, maximum, and minimum cardiac weights were 361, 440, and 225 grams, respectively. Seven (78 per cent) of the patients had dilated, thin, flabby

TABLE IV. NECROPSY OBSERVATIONS IN NINE CASES OF SICKLE-CELL ANEMIA

PATIENT	AGE (YR.)	SEX	NECROPSY FINDINGS			REMARKS
			HEART	LUNGS	LIVER	
1	17	F	Weight, 440 grams. Marked left ventricular dilatation. Marked interstitial edema. Sickling of erythrocytes	Grossly edematous. Polymorphonuclear infiltration about bronchi	Weight, 3,080 grams. Grossly brown homogeneous appearance. Microscopically small yellow crystalline deposits within hepatic cells	Died six days postoperatively
2	10	F	Weight, 225 grams. Marked dilatation of right auricle and ventricle. Flattening of trabecular carnae. Zenker's degeneration. Polymorphonuclear interstitial infiltration	Moderate obliterative endarteritis	Weight, 795 grams. Moderate chronic passive congestion	Died four days postoperatively following removal of thyroglossal duct cyst
3	32	M	Weight, 430 grams. Marked dilatation of right and left ventricles. Flabby myocardium. Obliterative endarteritis of coronary and pericardial vessels. Vacuolization of sarcoplasm	Pulmonary edema. Obliterative endarteritis of occasional pulmonary arteriole	Weight, 1,350 grams. Extreme collapse necrosis. Sickling present	Died in coma following fainting attacks. Congestive heart failure
4	25	F	Weight, 350 grams. Dilated right and left ventricles. Grossly beefy red. Interstitial edema	Obliterative endarteritis of occasional pulmonary arteriole	Extreme chronic passive congestion	Died two days postoperatively
5	22	M	Weight, 350 grams. Dilated right and left ventricles. Interstitial edema	Pulmonary edema, slight pulmonary arteriolar thrombosis	Weight, 1,450 grams. Firm fatty change	Died following laparotomy for supposed ruptured peptic ulcer
6	23	M	Weight, 370 grams. Right and left ventricular dilatation. Heart beefy red	Pulmonary edema	Weight, 3,200 grams. Slate brown	Died five hours after blood transfusion
7	30	M	Weight, 390 grams. Right and left ventricular dilatation. Interstitial edema. Vacuolated sarcoplasm	500 c.c. of pleural effusion bilaterally. Marked pulmonary edema	Weight, 1,680 grams. Extreme chronic passive congestion	Congestive heart failure
8	35	M	Weight, 360 grams. Dilated right auricle and ventricle. Myocardial degeneration	Thrombosis of pulmonary arterioles in some areas	Nutmeg appearance	Congestive heart failure
9	18	F	Right ventricular dilatation. Myocardial degeneration	Pulmonary edema. Moderate thrombosis of pulmonary arterioles	Hepatomegaly with infarction	Died twelve hours postoperatively

hearts, and an equal number showed degenerative changes in the myocardium. Myocardial degeneration was evidenced by vacuolization of the sarcoplasm, disappearance of the muscle striation, and Zenker's degeneration of the myofibrils. Five patients of the autopsy series (55 per cent) had definite dilatation of both the right and left ventricles. Three (35 per cent) had dilatation of the right ventricle and one (11 per cent) had dilatation of the left ventricle alone.

The muscle fibers were separated by edema fluid, with or without an increase in the amount of interstitial tissue, in three (33 per cent) of the cases.

In one instance (Patient 3, Table IV) there was obliterative endarteritis of one of the small branches of the coronary artery. In the same case, a pericardial vessel showed occlusion from thrombosis and endarteritis.

The pulmonary arterial vessels showed endarteritis in varying degrees in six (66 per cent) of the cases. The degree of pulmonary endarteritis and thrombosis was for the most part slight, but was occasionally moderate in degree. In no instance was it marked. Sickling of the erythrocytes was frequently demonstrated within the pulmonary vessels. Six (66 per cent) of the necropsy series showed marked pulmonary edema, both grossly and microscopically. Only one patient (11 per cent) had pleural effusion. This patient (Patient 7, Table IV) had 500 c.c. of straw-colored fluid in each pleural cavity.

The mean, maximum, and minimum weights of the livers were 1,926, 3,200, and 795 grams, respectively. The livers showed chronic passive congestion in six (66 per cent) of the cases. In two cases (Patients 3 and 7, Table IV) hepatic cell necrosis was so severe that only about 25 per cent of the hepatic cells were definitely distinguishable.

III. *The Electrocardiogram.*—The results of the routine analysis of the electrocardiograms of twenty-five patients are shown in Table V. Precordial leads were recorded in the majority, but not in all, of the twenty-five cases.

TABLE V. ELECTROCARDIOGRAPHIC DATA IN TWENTY-FIVE CASES OF SICKLE-CELL ANEMIA

(Each compartment contains mean, maximum, and minimum values for each component of the electrocardiogram.)

LEAD	P		P-R	QRS				S-T	T	Q-T
	DURATION (SEC.)	AMPLITUDE (MM.)	INTERVAL (SEC.)	DURATION (SEC.)	AMPLITUDE Q (MM.)	AMPLITUDE R (MM.)	AMPLITUDE S (MM.)	SEGMENT (SEC.)	AMPLITUDE (MM.)	INTERVAL (SEC.)
I	0.084	0.950	0.153	0.065	0.624	10.680	1.220	0.094	1.684	0.339
	0.120	1.800	0.190	0.080	3.000	15.000	9.000	0.160	4.000	0.420
	0.040	0.120	0.120	0.050	0.000	4.000	0.000	0.030	0.200	0.280
II	0.096	1.204	0.152	0.065	0.120	14.320	0.960	0.092	2.576	0.316
	0.120	2.200	0.190	0.100	2.000	22.000	5.000	0.160	6.200	0.420
	0.000	0.000	0.130	0.040	0.000	4.000	0.000	0.000	0.500	0.280
III	0.056	0.264	0.153	0.066	1.080	6.780	1.256	0.108	1.036	0.323
	0.110	1.700	0.190	0.080	5.000	15.000	10.000	0.180	3.000	0.420
	0.000	-0.600	0.120	0.050	0.000	1.000	0.000	0.000	-0.400	0.280
CF_1	0.065	0.500	0.156	0.081	0.000	4.610	16.450	0.059	-3.410	0.350
	0.100	1.500	0.190	0.100	0.000	10.000	30.000	0.120	-6.000	0.400
	0.040	-2.00	0.120	0.070	0.000	2.000	7.500	0.040	-1.100	0.320
CF_2	0.073	0.440	0.154	0.081	0.111	9.331	24.390	0.084	-3.633	0.349
	0.110	1.000	0.190	0.100	1.000	14.000	33.000	0.120	1.000	0.400
	0.040	-0.300	0.120	0.070	0.000	4.000	18.500	0.020	-8.000	0.320
CF_3	0.054	0.225	0.144	0.081	0.125	15.000	11.500	0.072	-1.501	0.352
	0.060	0.500	0.190	0.100	1.000	18.000	26.000	0.120	5.000	0.400
	0.000	-0.200	0.130	0.070	0.000	5.000	2.000	0.000	-2.500	0.320
CF_4	0.050	0.200	0.154	0.011	1.380	15,125	6.777	0.066	1.222	0.349
	0.100	0.500	0.190	0.100	3.000	22.000	15.000	0.120	8.000	0.400
	0.040	-0.200	0.120	0.060	0.000	5.000	1.000	0.000	-3.000	0.320
CF_5	0.045	0.240	0.154	0.081	2.350	19.200	2.200	-0.044	2.330	0.350
	0.100	1.000	0.190	0.100	5.000	34.000	10.000	0.160	6.000	0.400
	0.000	-0.200	0.120	0.070	1.000	6.000	0.000	0.000	0.000	0.320
IVF	0.037	0.300	0.156	0.070	2.910	24.430	9.700	0.056	1.555	0.322
	0.080	1.000	0.190	0.100	16.000	30.000	24.000	0.140	14.000	0.400
	0.000	-0.200	0.130	0.050	0.000	7.000	0.000	0.000	-10.000	0.280

P Wave.—The mean value for the duration of the P wave was 0.096 second in Lead II; the maximum was 0.12 second. (The normal average for adults is 0.08 second, and varies between 0.06 and 0.11 second. The upper limit of normal is considered to be 0.10 second.) Only one patient (Patient 6, Table I) exceeded the upper limit of normal.

The greatest amplitude of the P waves was present in Lead II. The average amplitudes for Leads I, II, and III were 0.95, 1.20, and 0.26 mm., respectively. (The average normal

amplitudes are 0.55, 1.25, and 0.80 mm., respectively. The upper limits of normal amplitudes are considered to be 1.1, 2.5, and 2 mm., respectively, for Leads I, II, and III.) In five (20 per cent) of the cases of active sickle-cell anemia the height of the P wave in Lead I was greater than 1 millimeter.

There was slight notching of the apex of the P wave in five (20 per cent) of the cases. In no instance did the notch return as far as halfway to the isoelectric line. (Slight notching occurs in about 32 per cent of normal subjects.)

The P wave was diphasic or inverted in Lead CF_1 in five (15 per cent) of the cases in which CF_1 leads were taken. The P wave was negative in Lead IVF in two (20 per cent) of the cases. The average amplitude of P in this lead was 0.3 millimeter. The percentages of patients with diphasic or inverted T waves in Leads CF_2, CF_3, CF_4, and CF_5 were 33, 25, 22, and 22 per cent, respectively. Thus the P wave exceeded the upper limit of normal for duration in 4 per cent of the cases, and it exceeded the upper limit of normal for amplitude in 20 per cent.

P-R Interval.—The P-R interval in the twenty-five cases averaged 0.15 second, and varied between 0.19 and 0.12 second. (The normal, mean P-R interval is 0.15 second.) The average cardiac rate was 90 beats per minute, and the extremes were 60 and 125.

Six patients (patients 4, 10, 12, 14, 19, and 23, Table I) were 21 years of age or more. The average P-R interval of these patients was 0.15 second, and the extremes were 0.14 and 0.17. The cardiac rates varied between 57 and 84 beats per minute. In no instance did the P-R interval reach the upper limit of normal. Two of the patients were under 2 years of age and had normal P-R intervals.

The remaining seventeen patients were children ranging in age from 6 to 16 years. Their cardiac rates varied between 60 and 125 beats per minute. The average P-R interval for this group was 0.15 second, and the extremes were 0.13 and 0.19 second. The interval in three of these cases (Patients 6, 7, and 22, Table I) exceeded the upper limit of normal by 0.01, 0.02, and 0.02, respectively. Patient 5 reached, but did not exceed, the upper limit of normal of 0.17 second.

In the chest leads the interval was not significantly different from the standard leads. The average interval for all of the precordial leads was 0.15 second. The range extended from 0.12 to 0.19 second. Thus, of the entire twenty-five patients, three (12 per cent) had P-R intervals which exceeded the upper limit of normal.

QRS Complex.—In only one instance did the duration of the QRS interval reach, but did not exceed, the upper limit of normal (Patient 3). The duration of the QRS interval of the two infants was 0.06 and 0.05 second, respectively. In the adults, the average duration was 0.07 second, and varied between 0.06 and 0.08 second. In the remainder, the child-adolescent group, the average duration was 0.06 second, and it varied between 0.05 and 0.08 second. (The upper limit of normal is 0.10 second.)

In the chest leads the duration of the QRS complex was slightly longer than in the standard leads. The average duration for the six chest leads was 0.08 second. The extremes were 0.05 and 0.10 second. Thus, in no instance was the QRS interval abnormally long.

Q Wave.—The amplitude of the Q wave in Lead I averaged 0.62 mm., and varied between 0 and 3. In Lead III the amplitude averaged 1.08 mm., and varied between 0 and 5. The maximum amplitudes in Leads I and III did not occur in cases of extreme right or left axis deviation. In Patients 2 and 12, Q_3 was more than one quarter the amplitude of the highest R wave of the standard leads. The duration of Q did not reach 0.02 second in any instance. In one instance the Q wave was present in all leads.

The Q wave was absent in all CF_1 leads. There was a progressive increase in the amplitude of the Q wave as the exploring electrode passed from the right to the left side of the precordium. The average Q wave in Lead IVF was 2.9 millimeters. The deepest Q wave in this lead measured 16 millimeters. In no case was the Q wave indicative of heart disease.

R Wave.—The highest R wave in the three standard leads measured 22 mm., and the lowest, 1 millimeter. The normal range is 1 to 23 millimeters. Notching of the R wave was present in 50 per cent of the cases in Lead III. In no instance did the duration of the R wave exceed 0.04 second.

The amplitude of the R wave averaged 4.6 mm. in CF_1. The amplitude of the R wave increased as the exploring electrode was moved from the right to the left side of the chest. In Lead IVF the average amplitude was 24.4 millimeters. The amplitude of the R waves in the chest leads did not exceed the upper limit of normal in any case. Thus the amplitude and duration of the R wave were not in any instance abnormal.

S Wave.—The deepest S wave in the three standard leads was studied. The average was 1.26 mm., and the extremes were 0 and 10.

In the chest leads the S waves were large in electrocardiograms taken on the right, and small in those taken on the left side of the chest. The average amplitude of the S wave in Leads CF_1, CF_2, CF_3, CF_4, CF_5, and IVF was 16.5, 24.4, 11.5, 6.8, 2.2, and 9.7 mm., respectively.

In Lead CF_1 the upper limit of normal of 20 mm. in amplitude was exceeded by three patients (30 per cent). In CF_2 it was exceeded in six cases (60 per cent), and in CF_3 it was exceeded in two cases (20 per cent). The maximum amplitude was 33 mm in CF_2.

The Electrical Axis of the QRS Complex.—The electrical axis of the QRS complex averaged 49.5 degrees, and varied from 0 to +125 degrees. Patient 16, Table I, had a deviation of +125 degrees. This patient was a 6-year-old girl who, at the time the electrocardiogram was taken, had an attack of pulmonary pain which was interpreted as the result of pulmonary infarction. Serial electrocardiograms are shown in Fig. 1. The electrical axis was abnormal in only one (4 per cent) of the series. The deviation in this case was to the right.

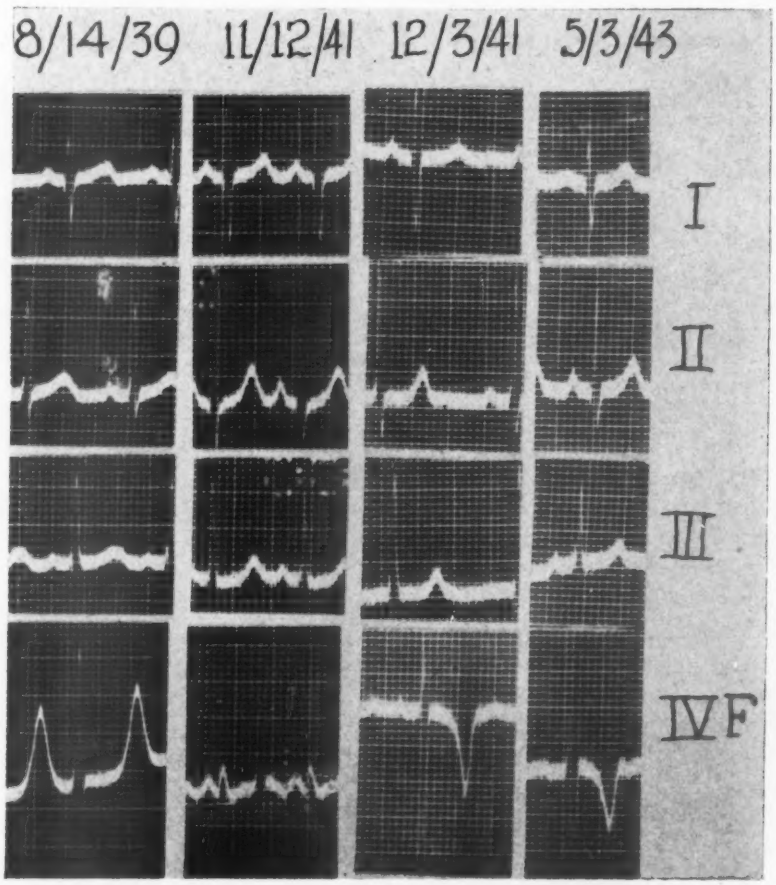

Fig. 1.—Serial electrocardiograms of Patient 16. There is right axis deviation (determined by measuring areas) of the QRS. This is the only instance of abnormal right axis deviation in this series. This figure shows a marked change in the T wave in IVF during the four years of follow-up.

S-T Segment.—The amplitude averaged 0.092 second in Lead II, and varied between 0 and 0.16 second. The average duration for males was 0.088 second, and the average cardiac rate was 87.1 beats per minute. The length of the segment for females averaged 0.096 second, and the average cardiac rate was 85.1 beats per minute. Those with the fastest rates had the shortest S-T segments.

The S-T segment in the chest leads did not vary significantly from the values indicated for the standard leads. In no instance was the segment greater than the upper limits of normal for the cardiac rate and sex. In no instance did the segment deviate 1 mm. or more from the isoelectric line in any lead.

T Wave.—The T waves were upright in all instances in Leads I and II, and in 78 per cent of the cases in Lead III. The average amplitude in Lead I was 1.7 mm., and the maximum was 4 millimeters. (The average amplitude in Leads I and II in normal subjects is 2 and 3 mm., respectively.) In Lead I the lowest T waves were encountered in Patients 12 and 22, who had amplitudes of 0.5 and 0.2 mm., respectively. The average amplitude for the twenty-five patients in Lead II was 2.6, and the maximum amplitude was 6.2, millimeters. (The normal mean is 3 millimeters.) Patients 22 and 23 had T waves in Lead II which were 0.5 and 0.8 mm., respectively. In the remaining cases the T waves in Lead II were over 1 mm. in amplitude. The average amplitude in Lead III was 1, and the maximum, 3, millimeters. (The mean for normals is 1.2 millimeters.) One patient, Patient 25, had a negative T wave in Lead III of -0.4 millimeter. Two patients, 1 and 20, had diphasic T waves in this lead. None of the T waves were sharply inverted in the standard leads.

In Patients 12, 21, and 22, T_3 was slightly higher than T_1. The electrical axes of the QRS in these cases were 61, 0, and 53 degrees, respectively. Patient 21 had a T_1 which measured 1 mm., and T_3 measured 2.1. All patients except this one had a QRS axis greater than 30 degrees. In Case 22 the highest T wave of the three leads was 0.5 millimeter. All other patients had T waves of 1.3 mm. or more. Ashman found that only seven of one hundred normal subjects had T waves with the greatest amplitude in all three leads of 1.5 mm. or less. Notched T waves were noted in Case 25. Rounding of the T waves was present in Case 21.

In the chest leads, the average amplitude of the T waves in Leads CF_1, CF_2, and CF_3 was -3.4, -3.6, and -1.5 mm., respectively. In Leads CF_4, CF_5, and IVF the averages were 1.2, 2.3, and 1.6 mm., respectively. In Leads CF_4 and IVF the T waves were inverted or diphasic in four cases (40 per cent), whereas, in CF_5, the T wave was diphasic in two instances (20 per cent). In only one instance was the amplitude of T greater than the normal value of 13 mm. for men, or 9 mm. for women. Thus, the T waves were abnormally low in one case in the standard leads, and the T wave was slightly increased in amplitude in Lead IVF. In Leads CF_4 and IVF the T waves were inverted or diphasic in four, or 40 per cent, of the subjects.

Q-T Interval.—When sinus arrhythmia was marked, the averages of more than one interval were recorded. The Q-T interval exceeded the normal in one instance by 0.05 second.

ELECTROCARDIOGRAPHIC CHANGES IN FOUR CASES WITH SERIAL ELECTROCARDIOGRAMS

The electrocardiogram was recorded serially in four cases over periods of observation varying from three to four years. Only one showed any significant changes, which are as follows:

In Case 16, serial electrocardiograms (Fig. 1) showed cardiac rates that varied between 88 and 125 beats per minute. The P waves and the P-R and Q-T intervals were within normal limits. There was definite right axis deviation (areas). The T waves in Leads IVF were upright in the first two electrocardiograms. The electrocardiograms taken Dec. 3, 1941, and May 3, 1943, had sharply inverted T waves in Lead IVF. There was no significant shift of the S-T segment.

DISCUSSION

It is apparent that sickle-cell anemia heart disease is essentially a disease of young people. The average age was 13 years for the living group, and 24 years for the autopsy group. The youthful age at which sickle-cell anemia cardiac disease occurs accounts for the frequent confusion with rheumatic heart disease and congenital heart disease.

Cardiac enlargement was almost universal in these cases, as ascertained fluoroscopically, roentgenographically, and at necropsy.

The type of cardiac enlargement may frequently aid in differentiating sickle-cell anemia heart disease from rheumatic mitral stenosis or other types of heart disease. In no instance in the cases of heart disease due to sickle-cell anemia was there enlargement of the left auricle. The electrocardiogram showed right axis deviation in only one instance. These facts aid in eliminating mitral

stenosis. The pulmonary conus was frequently prominent, and was particularly noticeable when there was evidence of pulmonary infarction. This produced a roentgenographic picture similar to that in cases of cor pulmonale produced by other types of pulmonary disease.

Cardiac murmurs occurred with great regularity. Mitral, pulmonary, and aortic murmurs, either systolic, or diastolic, or both, were encountered. A definite thrill was palpated in one case. This patient had mitral systolic and diastolic murmurs, and had no evidence of rheumatic fever; the cardiac signs were explainable entirely as a result of sickle-cell anemia.

Dyspnea on exertion was a common manifestation. Cardiac enlargement, a rapid pulse rate, fine, moist râles in the lungs, hepatomegaly, and edema of the ankles suggested right and left ventricular failure. All of these abnormalities, however, were often explainable as a result of severe anemia, pulmonary infarction, and hepatic changes due to sickle-cell disease. Severe right or left ventricular congestive heart failure, with severe orthopnea, was not encountered in any of the cases of this series. The presence of the sickle-cell anemia always made it difficult to evaluate the degree of cardiac decompensation because the disease itself may simulate this condition (vide supra).

Severe precordial pain, like orthopnea, was a relatively infrequent complaint. When it occurred it was difficult to ascertain its mechanism, that is, whether it was due to coronary arteritis from sickle-cell anemia, anemia per se, or other states, such as pulmonary crises due to sickle-cell anemia.

The pathologic changes in the myocardium consisted of marked interstitial edema, degeneration of the sarcoplasm, and thinning and dilatation of the right auricle and ventricle. In one case, there was endarteritis of the coronary arterioles and arteries of the pericardium. Over half (66 per cent) of the autopsied patients had endarteritis of the pulmonary vessels, although this was slight in many cases. Pulmonary edema was common. Hepatomegaly was not uncommon, and was probably caused by chronic passive congestion and specific changes due to sickle-cell anemia.

Anemia alone is probably an important factor in the production of the signs and symptoms and pathologic changes encountered in this disease. In all severe anemias the reduction in hemoglobin is accompanied by certain compensatory mechanisms, such as a greater oxygen difference in arterial and venous blood, increased cardiac output, increased pulse rate, and a more rapid circulation time. All of these tend to keep up the oxygen supply to the tissues. Because of the increased work of the heart, which is supplied by an insufficient amount of oxygen, we may expect enlargement of the heart in severe anemias. This enlargement, including both dilatation and hypertrophy, is commonly associated with fatty degeneration. Such changes have been reported many times in a variety of severe anemias, including chlorosis,[11] aplastic anemias, and pernicious anemia, especially before the advent of liver therapy. There are, however, certain changes which are not due to the anemia per se, but are peculiar to sickle-cell anemia. For example, changes in the heart may be manifestations of arteritis and endarteritis with thrombosis. Such vessel changes and the resultant parenchymal changes in the organs nourished by these vessels affect the central and peripheral circulation. These and other pathologic manifestations make sickle-cell anemia unique among the anemias.

Anemia, although neglected as a definite cause of heart disease, is a well-known one. The criteria laid down by the Criteria Committee of the New York Heart Association for the diagnosis of heart disease due to anemia are:

1. The presence of marked anemia.

2. Disturbances of cardiac function.

3. Disappearance of signs and symptoms after relief of the anemia.

In many anemias these criteria are met. In sickle-cell anemia one deals with an anemia which is, using present-day methods, somewhat refractory to treatment. Criterion *3* cannot be satisfactorily met except for short periods of time. In this disease severe grades of anemia remain, and result in severe strain upon the heart for years. One cannot expect these changes to be reversible unless the anemia is reversible. It is obvious that, in sickle-cell anemia, the same factors are at work as in other anemias, and, in addition, the changes are accentuated by the refractory nature of the anemia, coupled with the fact that it is compatible with many years of life. The cause and effect relationship of the anemia and cardiac abnormalities cannot be denied.

In addition to what is noted above, certain cardiac changes occur which differ somewhat from the usual cardiac expressions of ordinary clinical forms of anemia. These include the rather constant enlargement of the right ventricle and pulmonary conus. Yater and Hausman[4] and Klinefelter[6] have stated that this may be associated with pulmonary vascular lesions. It has, however, been demonstrated that similar changes occur in severe and prolonged anemias of other types.[10] Goldstein and Boas,[11] in 1927, reported that twenty-three of thirty-nine patients with pernicious anemia had cardiac enlargement. In twelve who came to autopsy there was dilatation of all chambers, and, in four, definite enlargement of the pulmonary conus. Their incidence of patients with cardiac enlargement was 57 per cent of the series, and is slightly less than that encountered in our series. They offered no explanation for the relative frequency of right ventricular dilatation in their cases. Such observations indicate that heart disease and right ventricular enlargement appear in other types of anemia, and are not yet explained entirely as a result of pulmonary changes. In fact, the pulmonary changes encountered in this series did not seem to be of sufficient degree consistently to produce the picture of cor pulmonale. In this series the left and right ventricles were enlarged, and evidence of left ventricular failure was as frequent as was evidence of right ventricular failure. The normal axis deviation of the QRS complexes, except in isolated cases, as well as the normal anatomic axis, perhaps indicates that the anemia per se is the important and usual cause of the clinical and pathologic evidence of cardiac disease in this disease, and not pulmonary or coronary arteritis. In unusual instances pulmonary arteritis may produce pulmonary heart disease, as was probably the case in Patient 16, Table I.

In many of the patients of this series no cardiac diagnosis was made until very late in the course of study. Hamman[3] emphasized the importance of being extremely cautious in making a nonanemia diagnosis of heart disease when studying a patient with sickle-cell anemia. One should be equally cautious in the interpretation of any sort of murmurs in the presence of severe, active, sickle-cell anemia, and wait until the anemia is under control.

Routine analysis of the electrocardiogram revealed only nonspecific, and rather inconsistent, changes. The electrocardiograms were slightly suggestive in 4 per cent of the cases, and definitely abnormal in another 16 per cent. Serial electrocardiograms sometimes showed additional evidence of myocardial change, although this was not the rule. There was no characteristic electrocardiographic pattern of the heart disease of patients with sickle-cell anemia. In general, the changes were those frequently encountered in cases of severe anemias or any toxic myocardial state. Cardiac arrhythmias of any type were distinctly

unusual. Premature beats were the only disturbances in cardiac mechanism encountered in the entire series.

Right axis deviation occurred in one case at a time when a clinical diagnosis of pulmonary infarction was made. Right axis deviation in this series was rarely an accompaniment of sickle-cell anemia heart disease; it occurred only once in twenty-five instances, in spite of the fact that enlargement of the right ventricle and pulmonary conus occurred in 86 per cent and 73 per cent of the cases, respectively. Also, in 88 per cent of the necropsy cases there was dilatation of the right ventricle, and none of these patients had had abnormal deviation of the QRS axis. Six of the necropsy patients showed mild or moderate pulmonary arteritis and thrombosis. None of these patients had abnormal axis deviation.

The P waves showed little deviation from the normal. They were occasionally of slightly increased amplitude and duration. The degree of notching was not greater than that found in normal subjects. In cases of rheumatic fever there is a somewhat greater tendency to widening and notching of the P waves.

The P-R interval surpassed the upper limits of normal in 12 per cent of the cases. However, in no instance was the P-R interval markedly prolonged, as sometimes occurs in other clinical states. In no instance was complete A-V block or bundle branch block seen. The duration of the QRS complex was within normal limits in all instances, and the Q-T interval was long in only one instance.

T waves suggestive of abnormalities were encountered in 20 per cent of the cases. These changes were generally borderline, and were not as a rule markedly abnormal. They varied from low T waves in Lead I to a low T_2, a T_3 which exceeded T_1 in amplitude in the presence of left axis deviation, a T wave of 0.5 mm. height in the tallest of any of the three standard leads, rounding of the T waves, or notching of the T waves. These changes were not secondary to alterations in the QRS complex, and, therefore, were probably the result of altered repolarization due to anemia, coronary arteritis, pulmonary thrombosis, or some state peculiar to sickle-cell anemia.

In the precordial leads, inversion of T was rather commonly encountered. Since most of these patients were in the younger groups, it was difficult to ascertain the significance of this. It may have been due to the position of the heart in relation to the precordial electrode. When the T waves had been upright in previous electrocardiograms and then became negative, the changes were of greater significance.

The high incidence of cardiac deaths at autopsy for the most part can be readily accounted for by the fact that severe myocardial disease was present in these cases. Anoxemia, shock, pulmonary or coronary thrombosis, surgical procedures, anesthesia, acute blood loss, sudden increase in blood volume, infection, and the like may precipitate congestive or anginal failure in these cases.

SUMMARY

The problem of sickle-cell anemia heart disease was studied in twenty-five carefully chosen cases of active sickle-cell anemia. The pathologic changes were studied in nine others. The problem of heart disease in patients with sickle-cell anemia was discussed from the clinical, pathologic, and electrocardiographic points of view.

The electrocardiograms were analyzed in the routine manner.

The disease occurred in young adults, and it was frequently confounded with rheumatic or congenital heart disease.

An outstanding feature of the cardiac disease was cardiac enlargement, which occurred in 95 per cent of the cases. The enlargement involved for the most part the left ventricle, the right ventricle, and the pulmonary conus. In no instance was undue enlargement of the left auricle observed.

Systolic and diastolic murmurs occurred at the aortic, pulmonic, and mitral areas. A thrill occurred in one case.

Dyspnea on exertion was a frequent complaint, but orthopnea was uncommon. The pathologic specimens showed arteritis of the pulmonary, pericardial, and coronary arteries in one case, and mild pulmonary thrombosis in six of the nine subjects autopsied.

Routine analysis of the electrocardiogram showed nothing characteristic of sickle-cell anemia heart disease. Significant changes in the electrocardiogram were seen in 20 per cent of the cases when single electrocardiograms were studied in the routine manner. Serial electrocardiograms showed very few changes over periods of approximately four years.

Definite right axis deviation occurred in only one case, although enlargement of the pulmonary conus or right ventricle was encountered in 73 and 88 per cent of the cases, respectively.

Premature beats were encountered in only two cases. No other cardiac arrhythmias, other than sinus arrhythmia, were seen.

The P waves showed about the same degree of notching as is encountered among normal subjects.

The P-R interval surpassed the upper limit of normal in 12 per cent of the cases. Complete A-V block and bundle branch block were not present in this series.

Only 4 per cent of the patients had a low T wave in Lead I.

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THE NORMAL HUMAN VENTRICULAR GRADIENT

V. The Relationship Between $\hat{A}_{QRS}$ and $\hat{G}$, and the Potential Variations of the Body Surface

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IN EARLIER papers of this series the spatial relationships between the longitudinal anatomic axis of the heart, the mean spatial QRS axis, and the spatial ventricular gradient were described.[1, 2] It was inferred from the effects of rotation of the ventricles about the three possible axes of rotation that, in persons of usual body build, the mean spatial QRS axis, $S\hat{A}_{QRS}$, commonly projects posteriorly as well as downward and toward the left, and that the spatial ventricular gradient of Wilson, $S\hat{G}$, although usually also directed downward and to the left, has a less backward direction. It was calculated that, on the average, the spatial angle between $S\hat{A}_{QRS}$ and $S\hat{G}$ is nearly 30 degrees; that between $S\hat{G}$ and $S\hat{H}$, the latter being the longitudinal anatomic axis of the ventricles, the spatial angle is about 60 degrees; and that 90 degrees separate $S\hat{A}_{QRS}$ and $S\hat{H}$. The three axes were found to lie very nearly in the same plane in the normal heart of the supine, or semirecumbent, person, without tachycardia. Spontaneous tachycardia, the erect posture, or both, sometimes caused deviation of $S\hat{G}$, usually moderate in extent. More recently, ouabain has been found sometimes to cause a similar deviation.[3]

In the earlier studies these, and other, conclusions were reached from a study of limb lead electrocardiograms. No special study was made of the distribution of the net QRS or QRS-T potentials over the body surface. If the conclusions reached in the previous papers were correct, the electrical evidence for the presence of a spatial angle between $S\hat{A}_{QRS}$ and $S\hat{G}$ should be obtainable by mapping the potential changes of the body surface. Furthermore, our earlier inferences regarding the cause of individual differences in the magnitude of the manifest mean QRS axis, A_{QRS}, should receive additional support if those inferences were correct.[3, 4] Incidentally, our results throw further light upon the question of the applicability of the principle of the Einthoven triangle in human electrocardiography.

METHODS

In the present study the potential changes at twenty-three points on the body surface were recorded on two patients with enlarged left ventricles, and on eight normal persons. The latter were chosen to obtain a sampling of subjects whose limb lead electrocardiograms were of contrasting types, and the positions of whose hearts differed widely. The indifferent electrode was the common terminal of Wilson, employed without the use of resistances, according to the method described by Goldberger.[5] The experimental subjects were in a semirecumbent position in a wheel chair when the curves were taken, with the exception of the two patients and one normal subject. The body surface points chosen for recording the potential changes are shown in Fig. 1, and need not be named. Since the method does not yield reliable results when the exploring electrode is much nearer to one than to the other electrodes of the common terminal, the potentials of the two arms and left leg were calculated from the three standard limb leads.[6] The net area of the QRS complex and also of QRS-T

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was estimated for each of the points. (As in the previous papers, the areas were recorded as units, and each was 4 microvolt-seconds. One unit is the area of a small rectangle on the film when the time lines indicate 0.04 second, and when a glavanometer deflection of 1 cm. indicates a potential difference of 1 mV.)

RESULTS

A typical diagram showing the distribution of the net potential of the QRS and QRS-T complexes is shown in Fig. 1. At each tested point the upper numeral is the net QRS area in 4 microvolt-second units, and the lower numeral is the net QRS-T area. A plus sign indicates that the net area was positive, and vice versa. As nearly as could be judged from the potential distribution, an isopotential line was drawn to mark zero potential difference between the points in the line and the common terminal. The negative area in the QRS diagram, that is, the region where all the upper numbers are marked by minus signs, marks the part of the body surface upon which the net QRS area is negative;

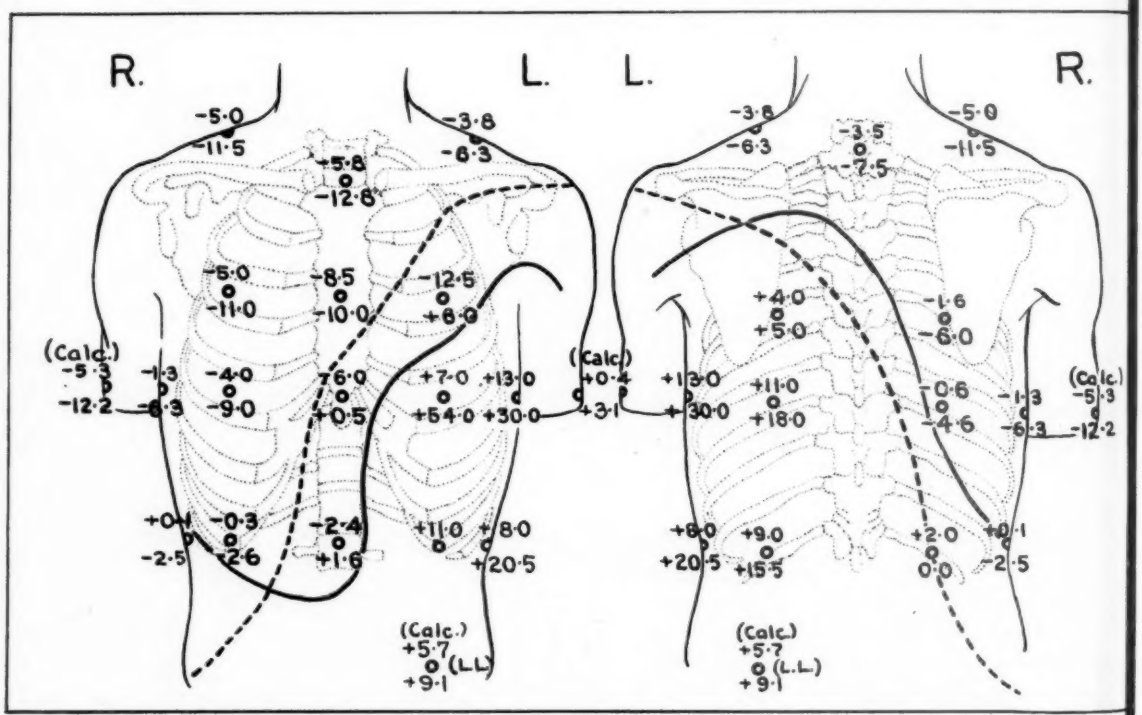

Fig. 1.—Subject 8. At each point marked by a small circle, the upper numeral is the net area, in 4 microvolt-second units, of the QRS complex; the lower numeral is the net area of QRS-T. A plus sign means that the net area was positive, relative to the common terminal, and a minus sign means that the net area was electrically negative. The solid line is the approximate line of zero potential difference between the chest potential and the common terminal for QRS, and the dotted line, similarly, is the approximate isopotential line for QRS-T.

and the positive area marks the region in which the same net area is positive relative to the common terminal. Similarly, the surface regions in which the net QRS-T area is negative and positive are shown by the lower numbers of each pair. A solid line separates the positive and negative QRS areas, and a dotted line separates the QRS-T areas. As previously reported for normal persons (lacking mirror-image dextrocardia), the right shoulder and arm are nearly always in the negative field of both the mean QRS and QRS-T axes, whereas either the left arm or the left leg may lie in either field.[7] One of our subjects (Fig. 4) was an exception.

It may be observed in Fig. 1 that a part of the positive field of QRS overlaps a part of the negative field of QRS-T or vice versa. A comparison of the lines shows that, on the front of the thorax, the line for QRS is below and to the left of the line for QRS-T, whereas on the back of the thorax, the QRS line lies above and to the right. In this subject, $\hat{A}_{QRS}$ and $\hat{G}$, the spatial axes as projected upon the frontal plane, were +63 degrees and +46 degrees, respectively. If the spatial axes coincided, the body surface fields should differ but little, if at all, in distribution. The existence of a large overlap demonstrates that the spatial axes do not coincide, but that the two spatial axes are separated by a spatial angle of fair magnitude.* Since the same kind of difference in the fields was found in all the normal subjects and in one of the patients, the results confirm the earlier conclusion. When the heart is normal the spatial angle cannot be accurately estimated from the chest potentials, yet the order of magnitude evidently agrees with the previous conclusion. The exceptional person, in whom very little difference in field distribution was found, had aortic insufficiency and a hypertrophied left ventricle.

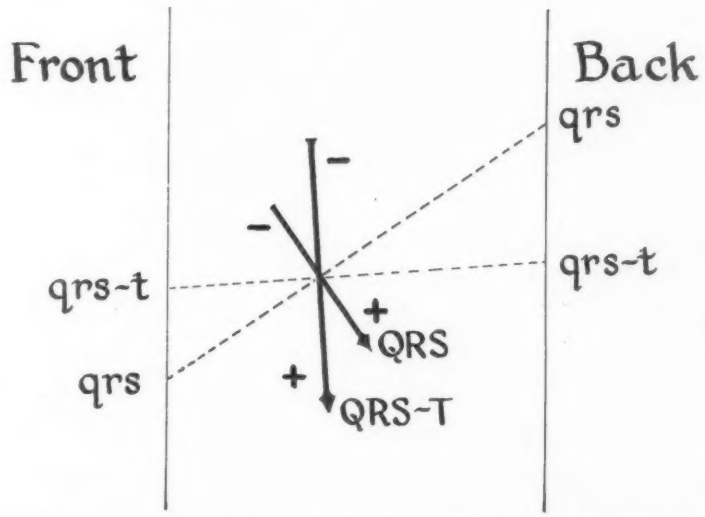

Fig. 2.—The vertical line marked "front" is the anterior chest surface, and the line marked "back" is the posterior chest surface. If the mean QRS axis has the direction shown, the isopotential lines, as shown in Fig. 1, will pass through the points marked *qrs*. These points are those at which a perpendicular to QRS reaches the surface of the thorax. The mean QRS-T axis typically points less dorsally than QRS, and the isopotential line would pass through the points marked *qrs-t*. The overlapping of the electrical fields of QRS and QRS-T, as shown in the other figures, is due to the different directions of QRS and QRS-T.

Since the spatial vectors, $S\hat{A}_{QRS}$ and $S\hat{G}$, are defined in terms of potential changes at the extremities, the vectors shown in this diagram cannot be correctly designated by those symbols.

Fig. 2 explains in diagrammatic fashion the reason for the observed difference in distribution of the electrical fields of the QRS and QRS-T complexes. When the body is viewed from the side, especially in the common case of a heart which is not strongly rotated about the longitudinal anatomic axis, the axis, $S\hat{A}_{QRS}$, is directed more posteriorly than $S\hat{G}$.[2] The lines drawn perpendicularly to the centers of the arrows representing the vectors should reach the body surface at the zero isopotential line. It will be observed that, on the front of the thorax, the point at which the perpendicular to the mean QRS touches the sur-

*This statement is based on the assumption that the polarized shells appearing within the myocardium are continuous, and that the intensity of polarization of each shell is the same at each part of the shell. Since there is good reason to believe that neither of these conditions obtains, the lines separating the regions in which the net QRS or QRS-T areas are of different sign do not represent accurately the projected boundaries upon the body surface of $S\hat{A}_{QRS}$ and $S\hat{G}$. The nearer the heart the surface point is, the greater the likelihood of error.

face is below the point at which the perpendicular to the mean QRS-T reaches the surface, whereas the reverse holds for the back of the thorax. This, of course, is the meaning of the field differences shown in Fig. 1. Since the vectors are directed to the left, as well as backward and downward, the zero isopotential lines on the thorax usually have an oblique, rather than a horizontal, direction. In every case the degree of this obliquity agreed reasonably well with the directions of the axes, as projected upon the frontal plane and as shown by the limb leads. The results in two other cases of contrasting types are given in Figs. 3 and 4. In these figures, as in Fig. 1, at each tested surface point the upper numeral is the net QRS potential, in 4 microvolt-second units, and the lower numeral is the net QRS-T potential. The isoelectric lines are drawn as before. The legend supplies other data.

A brief description of the results follows:

SUBJECT 1.—A middle-aged white man. Syphilitic aortic insufficiency and enlarged heart. $\hat{A}_{QRS}$ and $\hat{G}$ both at −20 degrees. Little overlapping of QRS and QRS-T fields, except slightly, in the usual sense, over precordium. Anteriorly, lines extend from lower rib margin on left to about the V_2 position, thence straight upward and across left shoulder near neck, then across back of neck and down to include most of right scapula, thence to right parasternal line, downward to lower costal margin, and to starting point. Back of left shoulder is at approximate center of positive fields, thus agreeing with limb leads.

SUBJECT 2.—Age and clinical condition like Subject 1. $\hat{A}_{QRS}$, +55 degrees; $\hat{G}$, +39 degrees. Fields, showing moderate overlap, agree well with relationships indicated by limb leads.

SUBJECT 3.—A white man about 60 years old. Chest deep, somewhat resonant, but no indication of heart disease. Illustrated in Fig. 4.

SUBJECT 4.—Young, adult, Negro male. No heart disease. Slender, but chest not flat. $\hat{A}_{QRS}$, +69 degrees; $\hat{G}$, +63 degrees; A_{QRS}, 6.7 units. G, 14 units. Isopotential lines oblique, in front and back, from left shoulder to above right lower costal margin. Fields suggest less backward projection of mean QRS vector than is suggested by its magnitude. Subject sat up for recording of posterior potentials.

SUBJECT 5.—White man, aged 40 years. No heart disease. Hypersthenic habitus, moderately obese. Illustrated in Fig. 3.

SUBJECT 6.—White man, aged 35 years. No heart disease. Sthenic habitus. $\hat{A}_{QRS}$, +82 degrees, magnitude, 6.7 units; $\hat{G}$, +59 degrees magnitude, 13.3 units. There is excellent agreement among the several data.

SUBJECT 7.—White man, aged, 20 years. No heart disease. Tall, sthenic, slightly obese. $\hat{A}_{QRS}$, +91 degrees, magnitude, 4.1 units; $\hat{G}$, +64 degrees, magnitude, 10.2 units. QRS line runs from left anterior axillary fold, at first transversely, thence downward to xiphoid, and then on a straight line to right anterior axillary fold. In back the line runs from right axilla upward, to left, above left scapula and down to left axilla. In keeping with the relatively small A_{QRS}, the indicated backward projection of the vector is considerable. There is a discrepancy of 11 degrees between the mean QRS direction, at about +80 degrees, suggested by the fields, and the +91 degrees given by the limb leads. The line for QRS-T is as usual, except that the band of overlap on the back is apparently less wide than in front—a usual finding.

SUBJECT 8.—White man, aged 21 years. No heart disease. Tall, sthenic. $\hat{A}_{QRS}$, +63 degrees, magnitude, 11 units; $\hat{G}$ +46 degrees, magnitude, 22.4 units. Illustrated in Fig. 1.

SUBJECT 9.—White man, aged 20 years. No heart disease. Sthenic. $\hat{A}_{QRS}$, +65 degrees, magnitude, 8 units; $\hat{G}$ +65 degrees magnitude, 17.5 units. Isopotential line for QRS-T oblique, and slightly closer to right shoulder than usual. Overlap slight on back. Otherwise, data fully consistent.

SUBJECT 10.—White man aged 26 years. No heart disease. $\hat{A}_{QRS}$, +83 degrees, magnitude, 7.8 units; $\hat{G}$, +69 degrees, magnitude, 10 units. Similar to Fig. 2, but the bands, as expected from vector directions, are more transverse, and the zones of overlapping are relatively narrow. Excellent agreement between indication of backward projection of $\hat{A}_{QRS}$ and the electric fields.

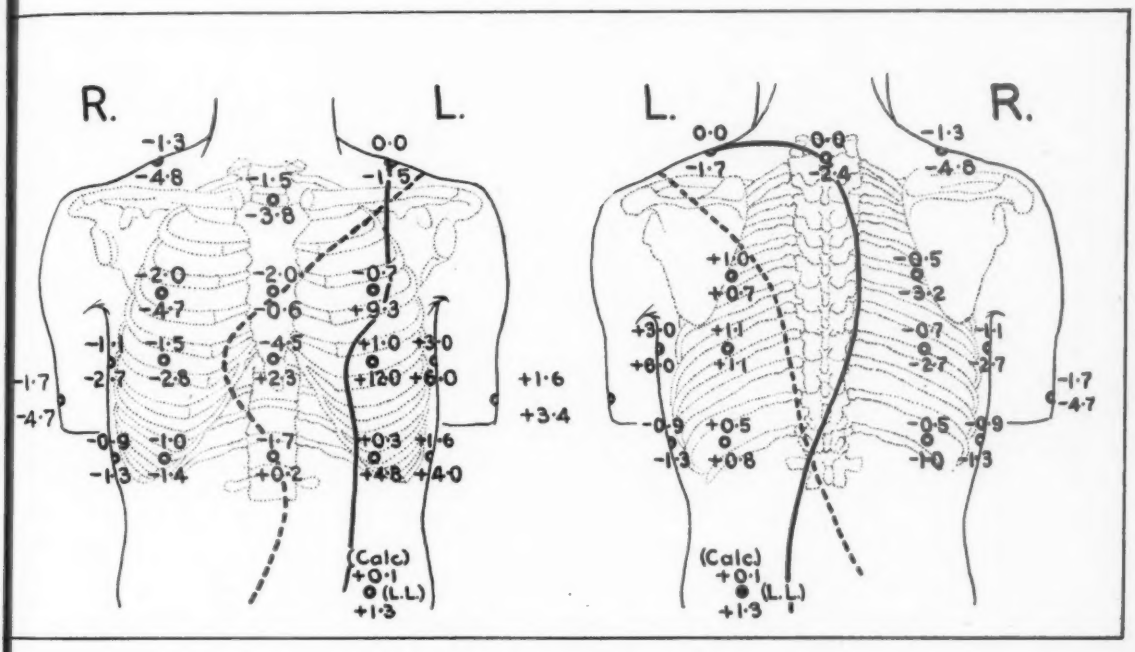

Fig. 3.—Subject 5. For interpretation, see Fig. 1.

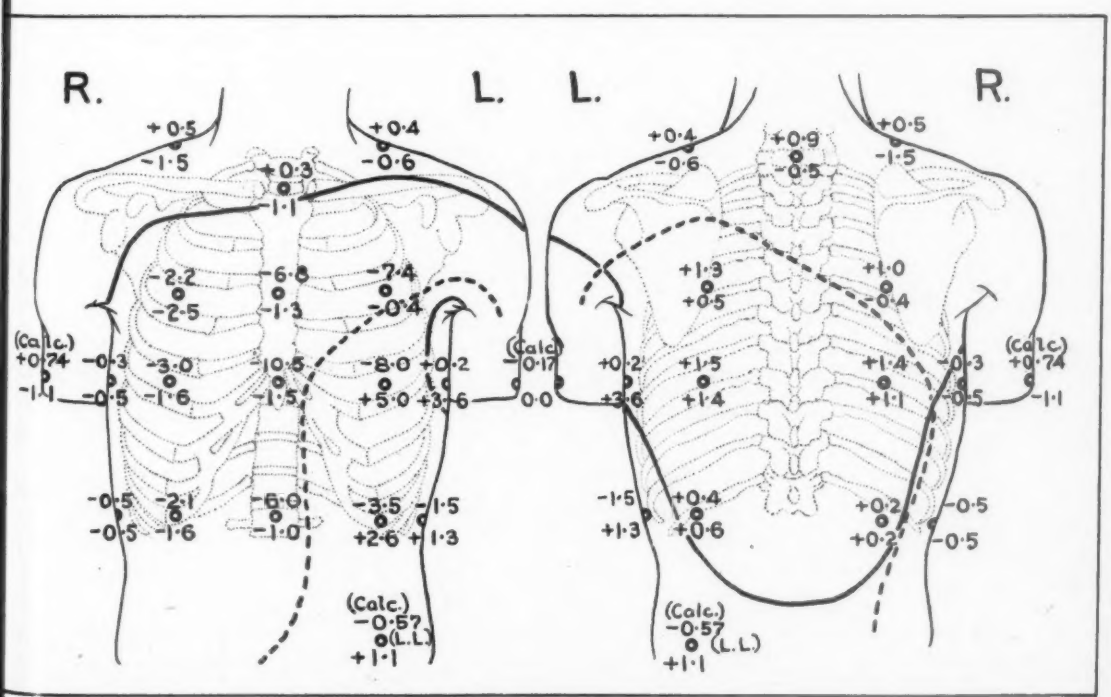

Fig. 4.—Subject 3. For interpretation, see Fig. 1.

A second purpose of the experiments was to seek additional evidence for or against the earlier interpretation placed upon individual differences in the magnitude, A_{QRS}, that is, the manifest magnitude of the mean QRS axis recorded in the limb leads. If that magnitude is zero, $S\hat{A}_{QRS}$ (the mean spatial axis) should point directly backward, perpendicular to the frontal plane.[2] In one of our subjects (Fig. 4), A_{QRS} was only 1.4 units in magnitude, and its direction was about −133 degrees. In this case, very evidently, as the distribution of the fields demonstrates, the previously stated interpretation of small A_{QRS} values is confirmed. However, the A_{QRS} value in the subject shown in Fig. 3 was only 3.3 units. If the mean spatial QRS axis, $S\hat{A}_{QRS}$, in this subject is 11.5 units, which was estimated to be the average value, then the vector should project back to form a 73 degree angle with the frontal plane. That the backward projection is not so great is probably indicated by the surface potential distribution. This case gives us the first objective evidence for a possibility we had previously suspected, namely, that, in certain persons, and especially in deep-chested, pyknic persons, such as this one, less than an average fraction of the potential change produced by the heart may be transmitted to the limb leads. The greater volume of body tissue may act much like fluid accumulation in the tissues, or the depth of the chest, by producing a relative forward displacement of the dipoles (Bayley, Wilson[8]), may reduce the magnitude of both $\hat{A}_{QRS}$ and $\hat{G}$. In another paper, now in press, we will show that in such cases the form of the QRS complex, rather than the magnitude, $\hat{A}_{QRS}$, affords the better indication of the direction of the spatial vector, $\hat{A}_{QRS}$. The spatial gradient, $S\hat{G}$, is apparently likewise reduced for the same reasons. There is, of course, a third way of accounting for some small magnitudes of the vectors, namely, that the *net* electromotive force generated by the heart is much less than the average in some cases. The form of the QRS complexes suggests that this factor, if present in Fig. 3, is of secondary importance.

The Potential of the Common Terminal.—A series of papers have advanced evidence which is believed to demonstrate the invalidity of the Einthoven triangle method as applied in human electrocardiography. The last paper in the series gives reasons for doubting that the potential of the common terminal of Wilson remains nearly at zero throughout the cardiac cycle.[9] Since our work is based upon the assumption that the mean potential of the common terminal is zero, or at the potential of the mid-points of the dipoles for both QRS and QRS-T, it is necessary for us to meet the objection. Fortunately our results enable us to draw some conclusions.

No one will quarrel with the self-evident statement that the electromotive forces responsible for the potential changes we are studying are produced in the heart. Therefore, subject to a possible discrepancy described in the footnote on page 699, if the body could be imagined as cut into two parts, with the surface cuts made along the isopotential lines of the figures, the section should pass through the heart. Inspection of our figures shows that this expectation is met for the QRS complex in eight of our ten cases; in two cases both the QRS and QRS-T section might miss the ventricular base by a centimeter or two, and in one other case (Fig. 1) only the QRS-T might miss it. If this is not due to the factor mentioned in the footnote (p. 699), it may imply that the mean potential of the common terminal is slightly negative, thus causing an apparent increase in the extent of the positive field. If this conclusion were to be accepted, then it is obvious from the potential differences shown by the limb leads that the mean potential of the right arm must be strongly negative during

inscription of the QRS or QRS-T complexes. If, as the authors quoted believe, the right arm undergoes relatively little change in potential during the inscription of QRS, the positive fieldes shown by our diagrams should appear much smaller and the negative fields much larger. In no case was there evidence for this, although, obviously, minor discrepancies could not be recognized.

Our conclusion is that, with respect to the *mean* electrical axes, no "enormous error" can be introduced by the Einthoven triangle method. That there may be minor errors, especially when the heart is very horizontal, is likely, as a later paper will point out; but the errors in normal chests are nearly negligible practically, and can be allowed for in analysis. With respect to the initial *instantaneous* axes of the QRS complex, it is possible that the error may be greater.

SUMMARY

The distribution of the net QRS and QRS-T potentials on the body surface supports the earlier conclusion that there is a spatial angle between the mean spatial QRS axis ($S\hat{A}_{QRS}$) and the mean spatial QRS-T axis ($S\hat{G}$). The earlier inference that small magnitudes of the mean QRS axis are due to a relatively backward projection of the mean spatial QRS axis ($S\hat{A}_{QRS}$) also receives added support, but the results indicate that some other factor or factors are sometimes also involved. Our results suggest further that no very large errors are involved in the use of the common terminal of Wilson as a zero reference point.

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DIPHTHERITIC MYOCARDITIS

With a Report of Two Cases

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THE heart is often affected in diphtheria with resultant electrocardiographic changes. This paper is concerned with the changes occurring in adults only.

In this global war, many of our soldiers are stationed in areas where diphtheria is endemic amongst the native population. Some of our troops consequently develop diphtheria. It is the practice of this hospital (general hospital overseas) to take serial electrocardiograms on all cases of diphtheria throughout the course of the disease.

Twelve cases of diphtheria have been diagnosed and treated; electrocardiographic changes were found in two, an incidence of 16.5 per cent cardiac involvement. Eggleston[1] described T-wave changes (similar to this series) as the most frequently observed electrocardiographic alteration in 16 per cent of his cases. During the stage of inversion, the T-wave changes may so closely simulate the inverted "coronary T wave" of myocardial infarction that this error in diagnosis can be made unless attention is paid to the S-T interval.

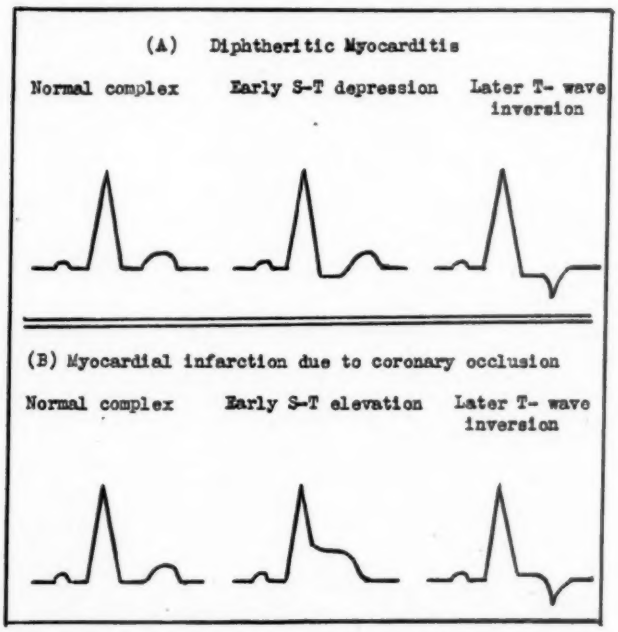

Fig. 1.—Schematic drawing illustrating the typical S-T and T-wave changes in (*A*) diphtheritic myocarditis and (*B*) myocardial infarction due to coronary occlusion.

The earliest electrocardiographic change observed in diphtheritic myocarditis (Fig. 1) is a depression of the S-T interval. The T wave then becomes lower in amplitude, isoelectric, diphasic, and finally inverted. The S-T interval always remains slightly depressed. This is in direct contrast to the S-T interval in myocardial infarction, where, after the initial marked elevation of the S-T interval and the subsequent inversion of the T waves, the S-T interval is always isoelectric or slightly above the isoelectric line.

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REPORT OF CASES

CASE 1.—A man, aged 22 years, complained of a sore throat and generalized aches and pains four days before admission to the hospital. Physical examination revealed what appeared to be an acute follicular tonsillitis which responded promptly to sulfadiazine by mouth. Five days later, while convalescing, he developed a sore throat, headache, and temperature of 101.8° F. Throat culture was positive for Klebs-Löffler bacilli and 40,000 units of diphtheria antitoxin were administered. Electrocardiogram (Fig. 2) taken on

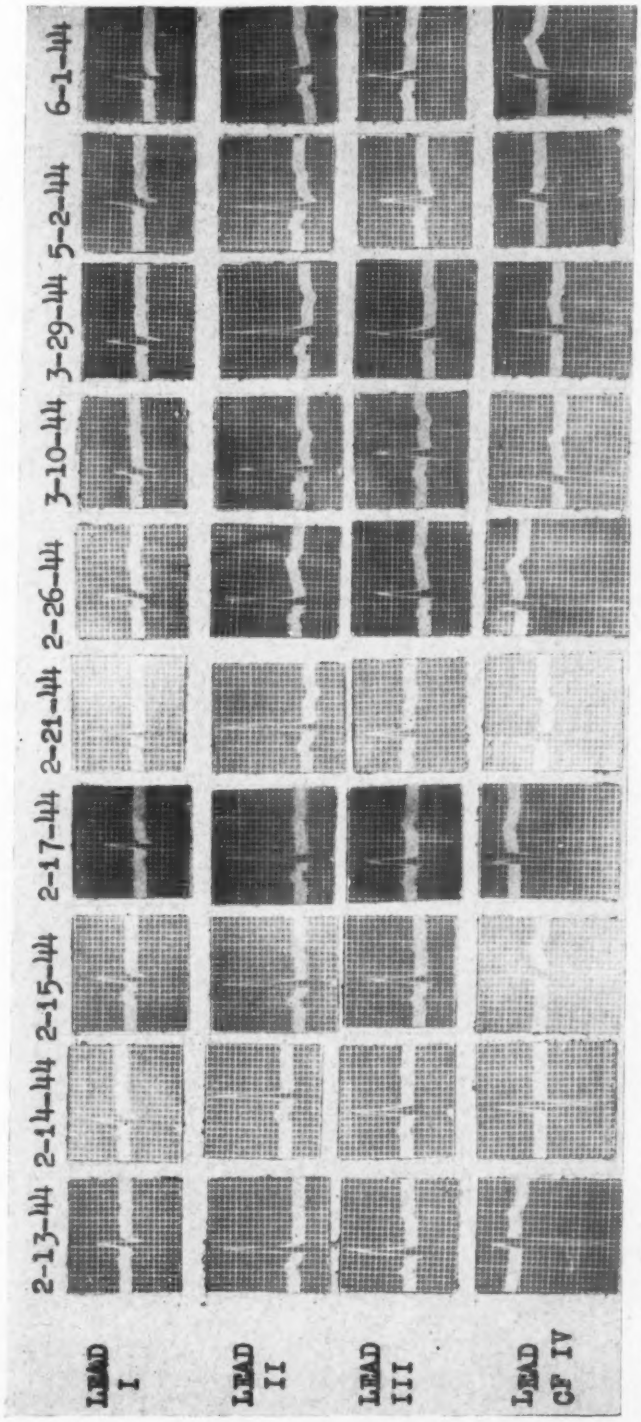

Fig. 2.—Case 1. Serial electrocardiograms, showing the typical changes of diphtheritic myocarditis in an adult with diphtheria.

Feb. 13, 1944, five days after the appearance of a membrane, showed definite changes. There was a prompt response to antitoxin, the throat cleared rapidly, and the patient remained symptom free. Because of the electrocardiographic changes present, he was kept quietly in bed and serial electrocardiograms were taken (Fig. 2). At no time were there any complaints referable to the cardiovascular system, physical examination of the heart was negative, and blood pressure and x-ray of the chest were normal. The electrocardiogram was considered normal on June 1, 1944, three and a half months after the first change was detected. He was returned to duty, resumed normal activities, and has re-

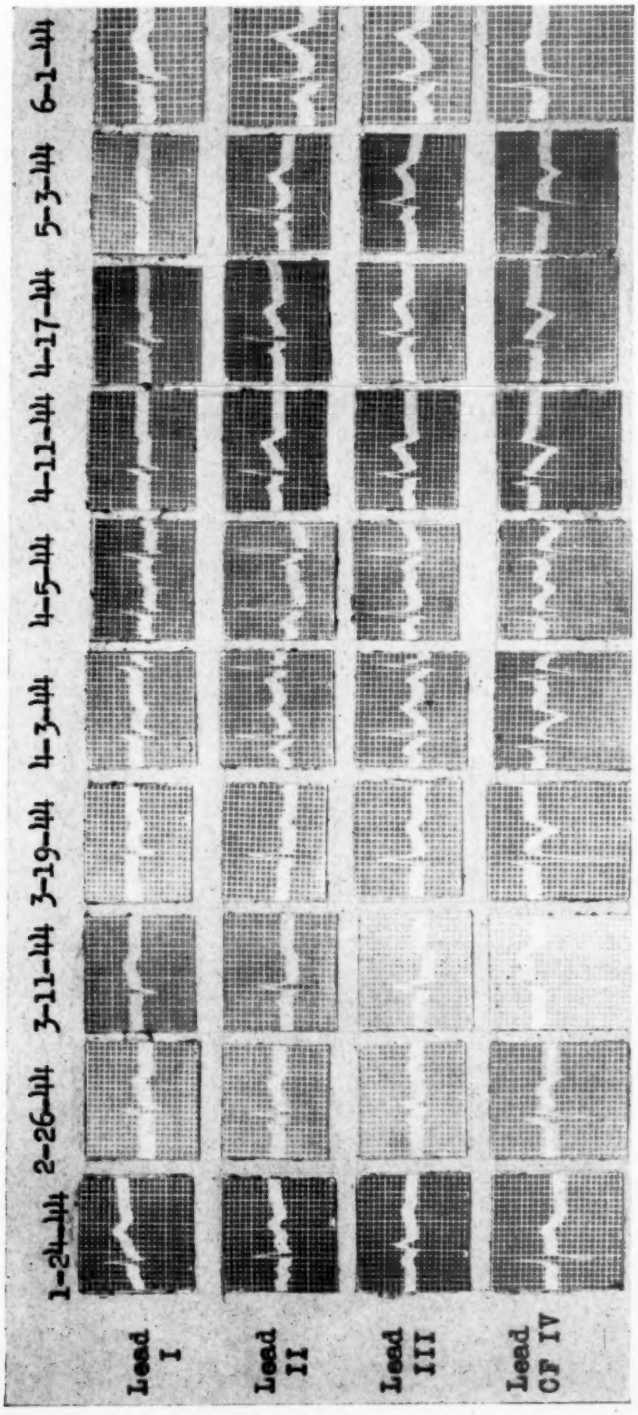

Fig. 3.—Case 2. Serial electrocardiograms, showing the typical changes of diphtheritic myocarditis in an adult with diphtheria.

mained symptom free. It cannot be stated with certainty whether or not this patient had diphtheria when he was first admitted to the hospital with what appeared to be an acute follicular tonsillitis. In view of the fact that there were other cases of diphtheria in the hospital at the time, it is possible and likely that the first evidence of "sore throat" was due to diphtheria.

CASE 2.—A man, aged 37 years, was admitted to the hospital on Jan. 24, 1944, with nasopharyngitis. A routine electrocardiogram was normal. While convalescing, he developed a perianal cellulitis, secondary to an internal hemorrhoid. This was treated conservatively. On Feb. 19, 1944, he had an epistaxis. Five days later (Feb. 24, 1944) he complained of a sore throat and the next day was found to have a dirty, gray membrane in the left nostril and an early membrane formation on both tonsils. Temperature was 102.6° F. A clinical diagnosis of diphtheria was made, nose and throat cultures were taken, and the patient was transferred to the isolation service and given 40,000 units of diphtheria antitoxin, intramuscularly. Nose and throat cultures were positive for Klebs-Löffler bacilli. The first electrocardiogram, taken Feb. 27, 1944, two days after the appearance of the membrane, was normal (Fig. 3). Temperature became normal on March 2, 1944, and the membrane disappeared on March 5, 1944. Nose and throat cultures, taken on March 9, and March 11, 1944, were still positive. A small follicle appeared on the left tonsil on March 12, 1944, and another dose of diphtheria antitoxin, 40,000 units, were given intramuscularly. An electrocardiogram, taken the next day, sixteen days after the appearance of a membrane, showed the first deviation from the normal, a depression of the S-T interval in Lead I and elevation in Lead IV. Electrocardiogram, taken on March 19, 1944, showed typical changes seen in diphtheritic myocarditis. The only clinical cardiac finding at this time was a persistent tachycardia with a rate of 120 per minute. Blood pressure was 120/70 and teleroentgenogram was normal. The patient then developed a classical, marked peripheral neuritis in all extremities with marked motor weakness. Marked apprehension and nervousness were present, and there was beginning weight loss. The nervousness, tachycardia, and weight loss suggested the clinical picture of hyperthyroidism. Unfortunately, there was no machine available to determine the basal metabolic rate. The patient was given a therapeutic test with lugol solution and, within a week, the pulse rate was normal, nervousness disappeared, and appetite returned. Lugol's solution was administered for another ten days and then discontinued. Serial electrocardiograms (Fig. 3) show the typical changes observed in this case with a return to an almost normal curve. The peripheral neuritis gradually improved and the patient was able to walk and get around before being evacuated to the zone of the interior.

COMMENT

The electrocardiographic changes observed in both cases described would indicate that there was severe and extensive myocardial involvement. At no time did these patients have any complaints referable to the cardiovascular system and, at no time, were there any clinical findings to suggest involvement of the heart. In both cases, the changes were reversible and shifting from day to day, suggesting that the changes observed are "toxic" in origin and not due to any structural damage to the heart muscle.

CONCLUSIONS

1. The electrocardiographic changes observed in two cases of diphtheria in adults are described. These changes conform to a type that is easily differentiated from those observed in myocardial infarction due to coronary artery occlusion.
2. The S-T interval is always depressed in diphtheritic myocarditis.
3. The changes are reversible and "shifting."
4. These effects are probably toxic in origin in diphtheritic myocarditis.
5. There was no clinical evidence of heart disease in either case described.

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THE USE OF THE AUGMENTED UNIPOLAR LEFT LEG LEAD IN THE DIFFERENTIATION OF THE NORMAL FROM ABNORMAL Q WAVE IN STANDARD LEAD III

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IN THE original descriptions of the electrocardiographic changes which follow localized myocardial injury[1] or coronary ligation in animals[2] and coronary occlusion in man,[3-5] emphasis was placed exclusively upon the changes in the ST-T segment. Although Q waves were present in the illustrations accompanying these reports, no comment was made regarding them, perhaps because of the known occurrence of Q_3 normally.[6-11] Passing mention was made of the presence of Q_3 in myocardial infarction by several authors during the next decade,[12-14] but the diagnostic significance was not appreciated until the work of Pardee,[15] in 1930. He concluded that a Q wave in Lead III which was 25 per cent or more of the tallest R wave in any of the three standard leads was of clinical significance, in curves which did not show right axis deviation, because of its frequent association with coronary artery disease and its rarity among normal persons. His observations were soon confirmed by others,[16-22] who found that a very high percentage of the electrocardiograms showing a Q_3 which conformed to Pardee's criteria or to slight modifications thereof was from patients with abnormal hearts, and a very small percentage was from persons with normal hearts. More recent studies, notably those of Short,[23] Stewart and Manning,[24] and Graybiel, et al.,[25] have indicated that a Pardee type of Q_3 which is indistinguishable from that associated with old posterior infarction is not infrequent in electrocardiograms from normal persons. It would thus appear that some additional method is needed for differentiating the Q_3 which often persists as a residue of old posterior infarction from the Q_3 which sometimes occurs normally.

Semidirect precordial leads, first described by Wolferth and Wood,[26] in 1932, but in use simultaneously by Wilson and his co-workers,[27] have aided greatly in the diagnosis of anterior infarction; they reveal many small infarcts that do not produce recognizable changes in the standard leads. Through the use of multiple precordial leads, Wilson, et al.,[27] in 1933, first advanced the explanation for the origin of the Q wave in myocardial infarction which is now generally accepted. They likened an infarcted area to a window or orifice in the ventricular wall through which potentials within the ventricular cavity are transmitted to the surface of the body. When the infarct is located in the anterior wall of the left ventricle, the potentials of the cavity are transmitted to the precordium and sometimes to the left arm, giving rise to abnormal Q and T waves in semidirect leads over the left ventricle, and sometimes in Lead I, as well. When the infarct is located in the posterior wall, abnormal Q and T waves appear in Leads II and III.

Semidirect esophageal leads provide a method for the study of lesions of the posterior wall which is comparable to the precordial leads for anterior wall lesions. An esophageal electrode was devised by Lieberson and Liberson,[28] and was applied by Hamilton and Nyboer[29] to the study of posterior infarction. Ac-

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cording to Nyboer,[30] a Q deflection in esophageal leads at the ventricular level (Lead E_V) is indicative of posterior infarction if it has a value of 0.4 mv. or is large in proportion to the R wave in Lead E_V.

Although esophageal leads are valuable, the procedure is unpleasant; if the patient is acutely ill, it may be dangerous. For these reasons, esophageal leads have not met with extensive clinical application.

In 1934, Wilson, et al.,[31, 32] presented a unique method of obtaining extremity potentials which were *unipolar*. They also made the significant observation that posterior infarctions usually face toward the left hind leg in the dog, and toward the left leg in man. Hamilton and Nyboer[29] and Kossmann and de la Chapelle[43] also noted that the electrocardiographic changes of posterior infarction may appear not only in Lead III and in esophageal leads from the ventricular level, but also in the left leg unipolar lead.

Goldberger[33] simplified Wilson's technique of obtaining unipolar precordial leads and also devised a method of augmenting by one and one-half times the hitherto small unipolar extremity potentials. He stated[34, 35] that small posterior infarctions may be shown by the left leg unipolar lead when there are no changes in the standard leads.

In a paper published after the completion of our study, Lyle[36] utilized the unipolar left leg potential of Wilson as a means of differentiating the normal Q_3 from that associated with posterior infarction. She studied twenty-nine cases in which there was a deep Q wave in standard Lead III and found that all ten patients who gave a history of coronary occlusion had a large Q wave in Lead V_F. She stated that it would be necessary to study a much larger number of cases to ascertain the normal limits of the Q wave in Lead V_F and to obtain conclusive statistical evidence of the diagnostic significance of the QRS pattern in this lead. The data presented in this communication provide further evidence bearing on this problem.

METHOD AND MATERIAL

Forty-nine persons with prominent Q or QS waves in Lead III were selected for study. In forty-five of the cases the electrocardiograms conformed to the criteria of Pardee:[15] (1) Q_3 was at least 25 per cent of the largest R in any of the three standard leads, (2) right axis deviation was not present, and (3) S_3 was absent. In a few of the cases, QRS_3 was represented by a QS complex rather than a QR complex, as originally specified by Pardee. In many of these cases it was difficult or impossible to express a definite opinion from the standard leads alone as to whether or not an old posterior infarct was present. One of the four remaining subjects (Case 15) had a prominent Q_3, together with right axis deviation resulting from pulmonary embolism. The other three subjects were controls with right axis deviation due to a vertical position of the heart, and had a Q_3 which ranged from 20 per cent to 33 per cent of the tallest R in the standard leads. One additional subject (Case 50) showed an RS complex instead of a Q wave in Lead III, but was included in the study because of ST-T changes typical of posterior infarction.

In all fifty cases, the following leads were taken: the three standard leads of Einthoven, six unipolar precordial leads (V_1 to V_6, inclusive), using the technique of Wilson, et al.,[37] or Goldberger,[33] and three augmented unipolar extremity potentials, according to the technique of Goldberger.[34*] The presence or absence of posterior infarction was positively established either by autopsy or by esophageal leads, supported by clinical data which in many cases included previous electrocardiograms. The electrical position of the heart was ascertained from the precordial and unipolar extremity potentials, using Wilson's[37] criteria.

*Goldberger's modification differs from Wilson's original central terminal only by the absence of the 5,000-ohm resistances. Precordial leads obtained by these two methods on the same patients were indistinguishable from one another; the two electrodes were completely interchangeable for this purpose, so far as we could ascertain. The advantage of the Goldberger electrode is that it can be used either for recording the unipolar precordial potentials or the augmented unipolar extremity potentials, whereas the original Wilson electrode does not lend itself to the latter.

Throughout this study, the Cambridge string galvanometer was used. Esophageal leads were taken with the subject in the recumbent position, using an improvised electrode made by passing a thin, insulated, braided copper wire through a Rehfuss tube, the tip of which served satisfactorily as a contact. The tube was marked off in 2.5 cm. segments, and an ordinary battery clamp was used as the contact at the proximal end. The tip could be readily passed nasally, and the procedure was not accompanied by any notable trauma. The indifferent electrode for the esophageal leads was the same as for the unipolar extremity and precordial leads. Our tracings agree very well with those of Nyboer,[30] and we have accepted his values of 35 to 40 cm. from the nares as the level of the auricles, and 45 to 55 cm. as the ventricular levels. In recording the measurements of the deflections, correction was made for errors in standardization.

PRESENTATION AND DISCUSSION OF RESULTS

A. *Mode of Establishing the Diagnosis.*—

1. Cases of Posterior Myocardial Infarction: A diagnosis of posterior infarction was made in a total of twenty-five cases (Table I). Four of these patients had a recent posterior infarct, as revealed by the electrocardiogram and confirmed at autopsy (Cases 13, 14, 16, and 19). Each of the remaining twenty-one patients had an old posterior infarct. Ten had been under our care during the acute attack months or years previously (Cases 2, 8, 20, 21, 22, 27, 31, 32, 46, and 47), at which time the classical signs were demonstrated in serial electrocardiograms. In addition, esophageal leads, taken at the time of this study, confirmed the presence of the old posterior infarct in all ten cases. The diagnosis was established in the other eleven cases (Cases 4, 6, 10, 12, 23, 24, 25, 35, 48, 49, and 50) by means of esophageal leads.

A summary of the esophageal lead data is given in Table I. According to Nyboer,[30] a Q_{EV} that exceeds 0.4 mv. is diagnostic of posterior infarction, especially if it is relatively large in proportion to the R wave in Lead E_V. Q_{EV} was 0.4 mv. or more in twenty of the twenty-two cases in this group in which esophageal leads were taken. The two remaining patients (Cases 10 and 48) showed Q waves in the esophageal leads which were less than 0.4 mv. in depth, measuring

TABLE I. ELECTROCARDIOGRAPHIC MEASUREMENTS IN TWENTY-FIVE CASES OF POSTERIOR INFARCTION

CASE NO.	QRS DUR^N.	Q_2			Q_3			%Q_3	Q_AV_F			Q_{EV}			DURATION OF INFARCT
		DUR^N.	VOLTAGE	%R_2	DUR^N.	VOLTAGE	%R_3	TALLEST R	DUR^N.	VOLTAGE	%R_AV_F	DUR^N.	VOLTAGE	%R_{EV}	
2	0.09	0.02	0.1	8	0.03	0.7	235	55	0.03	0.4	100	0.03	0.9	85	1 1/2 YEARS
4	0.08	—	—	—	0.04	0.9	225	55	0.02	0.45	110	0.03	0.6	40	3 MONTHS
6	0.08	0.01	0.1	15	0.02	0.35	70	65	0.02	0.3	60	0.05	0.55	INF.	OLD
8	0.10	0.03	0.1	30	0.05	0.4	INF.	60	0.03	0.25	200	0.03	0.4	100	2 YEARS
10	0.10	0.02	0.1	20	0.03	0.5	500	80	0.03	0.3	INF.	0.03	0.3	35	1 YEAR
12	0.08	0.02	0.1	10	0.03	0.7	175	55	0.03	0.3	60	0.03	0.7	INF.	2 MONTHS
13	0.07	0.02	0.15	100	0.04	0.9	200	100	0.03	0.5	125	ESOPHAGEAL LEADS NOT DONE			2 DAYS
14	0.09	0.03	0.1	100	0.02	0.15	INF.	50	0.02	0.1	135	ESOPHAGEAL LEADS NOT DONE			1 MONTH
16	0.14	—	—	—	0.04	1.0	INF.	90	0.04	0.7	INF.	ESOPHAGEAL LEADS NOT DONE			1 MONTH
19	0.07	0.02	0.3	60	0.03	0.8	INF.	80	0.03	0.4	INF.	0.04	1.5	500	2 WEEKS
20	0.10	0.03	0.4	90	0.03	0.7	200	160	0.03	0.6	120	0.02	0.55	45	7 MONTHS
21	0.11	0.02	0.3	85	0.03	0.55	200	75	0.03	0.4	200	0.04	0.7	70	1 1/2 YEARS
22	0.08	0.01	0.3	75	0.03	0.5	150	85	0.02	0.35	100	0.02	0.5	135	14 MONTHS
23	0.08	0.03	0.2	135	0.04	0.75	INF.	100	0.03	0.5	INF.	0.03	0.55	1100	OLD
24	0.11	0.02	0.2	45	0.05	1.1	275	80	0.05	0.5	200	0.02	0.45	100	OLD
25	0.09	0.02	0.3	30	0.03	0.55	60	55	0.03	0.4	42	0.03	0.85	35	1 YEAR
27	0.10	0.02	0.65	90	0.02	0.5	70	65	0.02	0.65	80	0.02	0.7	55	1 1/2 YEARS
31	0.07	0.02	0.1	15	0.02	0.4	INF.	40	0.02	0.3	INF.	0.03	1.0	100	8 MONTHS
32	0.08	0.03	0.5	125	0.03	0.8	400	100	0.03	0.8	400	0.04	1.4	1400	8 MONTHS
35	0.08	—	—	—	0.04	0.9	INF.	112	0.03	0.8	1600	0.03	0.8	INF.	OLD
46	0.07	—	—	—	0.02	0.3	100	25	—	—	—	0.03	0.6	100	13 MONTHS
47	0.11	—	—	—	0.04	0.6	INF.	60	—	—	—	0.03	1.7	115	10 MONTHS
48	0.07	0.04	0.25	INF.	0.04	0.4	INF.	135	0.04	0.2	INF.	0.03	0.25	75	7 MONTHS
49	0.07	0.02	0.35	40	0.035	0.55	85	50	0.025	0.4	35	0.03	0.9	55	7 MONTHS
50	0.10	—	—	—	—	—	—	—	—	—	—	—	—	—	OLD

0.3 and 0.25 mv., respectively. However, when the amplitude of Q_{EV} was considered in relation to R_{EV}, the ratios were 35 per cent and 75 per cent, respectively. In all of the remaining twenty cases in this group in which esophageal leads were made, Q_{EV} was also more than 25 per cent of R_{EV}, suggesting that this may be a more valuable criterion than the actual voltage of Q_{EV}.

2. Cases in Which There Was No Posterior Infarction: Posterior infarction was excluded in a total of twenty-five cases (Table II)—in three by autopsy and in the other twenty-two by esophageal leads. Q_{EV} was absent in sixteen of the twenty-two cases in which esophageal leads were classed as negative. In five cases (Cases 26, 30, 37, 42, and 43), Q_{EV} was considered insignificant because it was less than 0.4 mv. in amplitude and less than 25 per cent of R_{EV}. In the remaining case (Case 41), Q_{EV} was 0.6 mv. in amplitude, but was not considered a remnant of infarction because it was followed by an R_{EV} which measured 2.4 millivolts. The history was negative for coronary thrombosis in all but one of the cases in which posterior infarction was excluded by esophageal leads. The sole patient with a positive history (Case 42) was under our care during the acute attack, at which time serial electrocardiograms were diagnostic of anteroseptal infarction. Six months later, at the time of this study, electrocardiographic evidence of this infarct had completely disappeared. A small Q and a large R wave in Leads II and III, due to vertical position of the heart, were present in all electrocardiograms in this case, but posterior infarction was excluded by the absence of serial changes in QRS-$T_{2 \text{ and } 3}$ and by negative esophageal leads.

The difference in the esophageal lead pattern associated with posterior infarction and that in uninfarcted controls is illustrated by Figs. 1 and 2. Case 19 (Fig. 1) had typical electrocardiographic signs of posterior infarction in

TABLE II. ELECTROCARDIOGRAPHIC MEASUREMENTS IN TWENTY-FIVE CASES IN WHICH THERE WAS NO POSTERIOR INFARCTION

CASE No.	Q_2			Q_3			$\%Q_3$	Q_{AVF}			Q_{EV}			COMMENT
	DUR^N.	DUR^N.	VOLT.	$\%R_2$	DUR^N.	VOLT.	$\%R_3$	TALLEST R	DUR^N.	VOLT.	$\%R_{AVF}$	DUR^N.	VOLT.	$\%R_{EV}$	
1	0.11	—	—	—	0.02	1.1	185	65	—	—	—	—	—	—	SEMIHORIZONTAL HEART
3	0.10	—	—	—	0.04	0.8	400	55	—	—	—	—	—	—	" "
5	0.08	—	—	—	0.02	0.45	200	45	—	—	—	—	—	—	" "
7	0.06	—	—	—	0.03	0.9	INF.	45	—	—	—	—	—	—	" "
9	0.08	—	—	—	0.03	0.3	100	25	—	—	—	—	—	—	" "
11	0.09	—	—	—	0.02	0.5	250	60	—	—	—	—	—	—	" "
15	0.08	—	—	—	0.02	0.7	80	70	0.02	0.15	20	ESOPHAGEAL LEADS NOT DONE			NO INFARCT. PULMONARY EMBOLI (AUTOPSY)
17	0.09	—	—	—	0.02	0.7	1400	120	—	—	—	ESOPHAGEAL LEADS NOT DON E			NO INFARCT. L.V. HYPERTROPHY. PULMONARY EMBOLI (AUTOPSY)
18	0.11	—	—	—	0.03	0.75	INF.	100	—	—	—	ESOPHAGEAL LEADS NOT DONE			NO INFARCT. L.V. HYPERTROPHY. DIFFUSE FIBROSIS (AUTOPSY)
26	0.08	0.02	0.1	40	0.03	0.6	300	60	0.02	0.13	40	0.03	0.2	22	SEMIHORIZONTAL HEART
28	0.07	—	—	—	0.03	0.65	INF.	55	—	—	—	—	—	—	" "
29	0.06	0.02	0.1	25	0.02	0.3	300	60	0.02	0.2	65	—	—	—	POSTURAL $Q_{3?}$ WITH Q_AV_F
30	0.07	—	—	—	0.02	0.3	35	25	—	—	—	0.02	0.2	12	SEMI VERTICAL HEART
33	0.08	—	—	—	0.03	1.0	300	60	—	—	—	—	—	—	SEMIHORIZONTAL HEART
34	0.08	—	—	—	0.03	0.45	INF.	150	—	—	—	—	—	—	" "
36	0.08	—	—	—	0.03	0.4	400	60	—	—	—	—	—	—	" "
37	0.07	—	—	—	0.03	0.5	250	70	—	—	—	0.02	0.2	11	" "
38	0.06	—	—	—	0.02	0.4	200	45	—	—	—	—	—	—	" "
39	0.06	—	—	—	0.02	0.6	INF.	65	—	—	—	—	—	—	" " EARLY L.V. HYPERTROPHY
40	0.10	—	—	—	0.03	0.45	250	55	0.02	0.13	16	—	—	—	SEMIHORIZONTAL HEART
41	0.09	0.02	0.45	20	0.02	0.35	26	23	0.01	0.6	25	0.02	0.6	25	VERTICAL HEART
42	0.10	0.01	0.15	15	0.03	0.45	33	33	0.02	0.2	17	0.02	0.2	8	VERTICAL HEART. OLD ANTEROSEPTAL INFARCT.
43	0.08	0.01	0.1	8	0.02	0.3	20	20	0.02	0.2	14	0.02	0.3	12	VERTICAL HEART
44	0.12	—	—	—	0.06	0.7	2800	100	—	—	—	—	—	—	L.B.B.B. NO INFARCT
45	0.10	—	—	—	0.04	1.4	700	85	0.03	0.85	850	—	—	—	MARKED RESP. VARIATION. L.V. HYPERTROPHY

the esophageal leads and also in Leads II, III, and aV_F. The diagnosis was confirmed at autopsy. Case 38 (Fig. 2) was a representative normal control having a prominent Q wave in Lead III but no signs of infarct in the esophageal leads or in Lead aV_F.

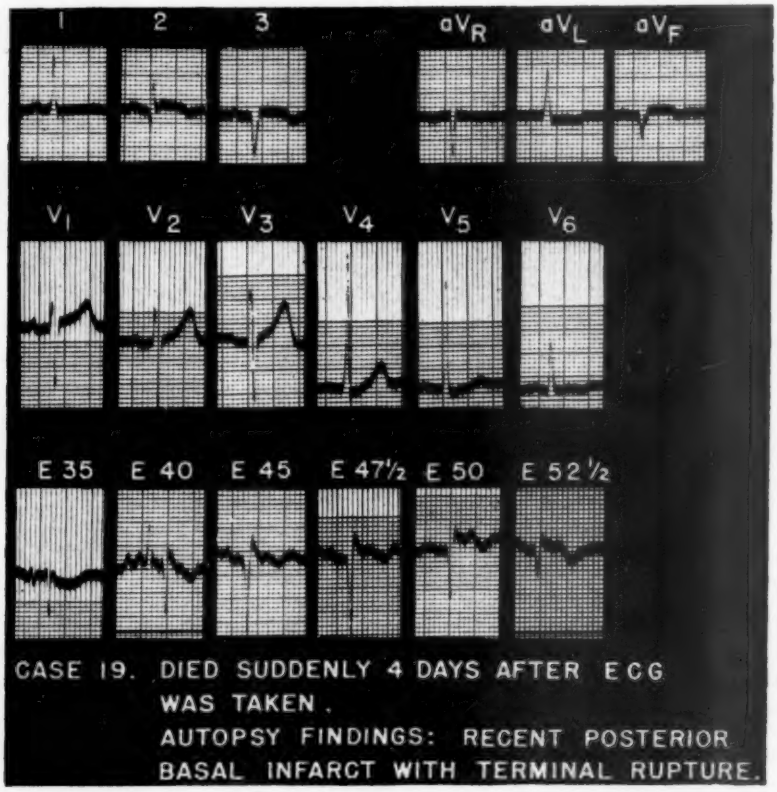


Fig. 1.

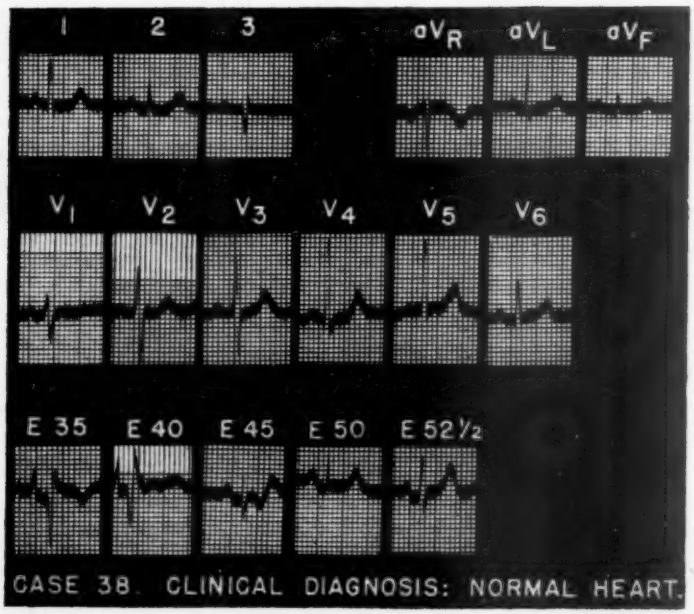


Fig. 2.

B. *Comparison of Standard Leads of Posterior Infarction With Those of Uninfarcted Controls.*—

1. Depth of Q_3 and Its Relation to the Tallest R: Measurements of the voltage of Q_3 and a ratio of the amplitude of Q_3 to that of the tallest R are recorded in Table I for the cases of posterior infarction and in Table II for the uninfarcted controls. Q_3 was 25 per cent or more of the tallest R in twenty-four of the twenty-five cases of posterior infarction, and varied in

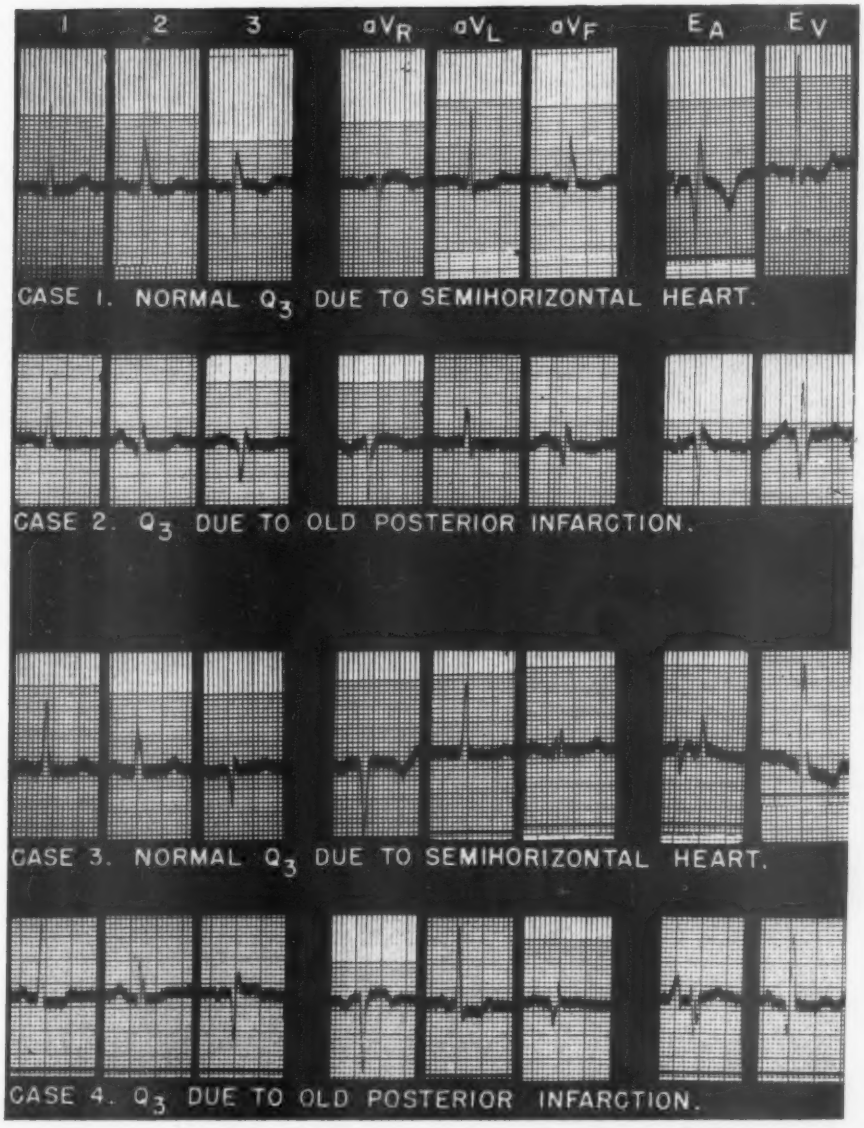


Fig. 3.—Use of augmented unipolar left leg potential (Lead aVR) to differentiate normal Q_3 from that due to posterior infarction.

depth from 0.15 to 1.1 millivolts. However, in all but two of the twenty-five persons without posterior infarction, Q_3 was entirely comparable, ranging from 0.3 to 1.4 mv. and amounting to 25 per cent or more of the tallest R wave. In the two exceptions (Cases 41 and 43) the ratio was borderline, being 23 per cent and 20 per cent, respectively. It is thus evident

that the two groups of cases cannot be differentiated on the basis of the depth of Q_3 or its relation to the tallest R wave.

2. Occurrence of Q_2 and Its Relation to R_2: A significant Q_2 (greater than 25 per cent of R_2, according to Durant[21]) was present in thirteen of the twenty-five patients with posterior infarction (Table I) and was found in only two of the twenty-five persons without infarction. Admittedly, this is a helpful finding when it does appear, but it is important to note that it was absent in nearly half of our patients with posterior infarction.

3. The Duration of Q_3: According to Bayley,[38] the duration of Q_3 is more important than its amplitude or its relation to the tallest R wave in the standard leads; his criterion for an abnormal Q_3 was a duration of 0.04 seconds or more.

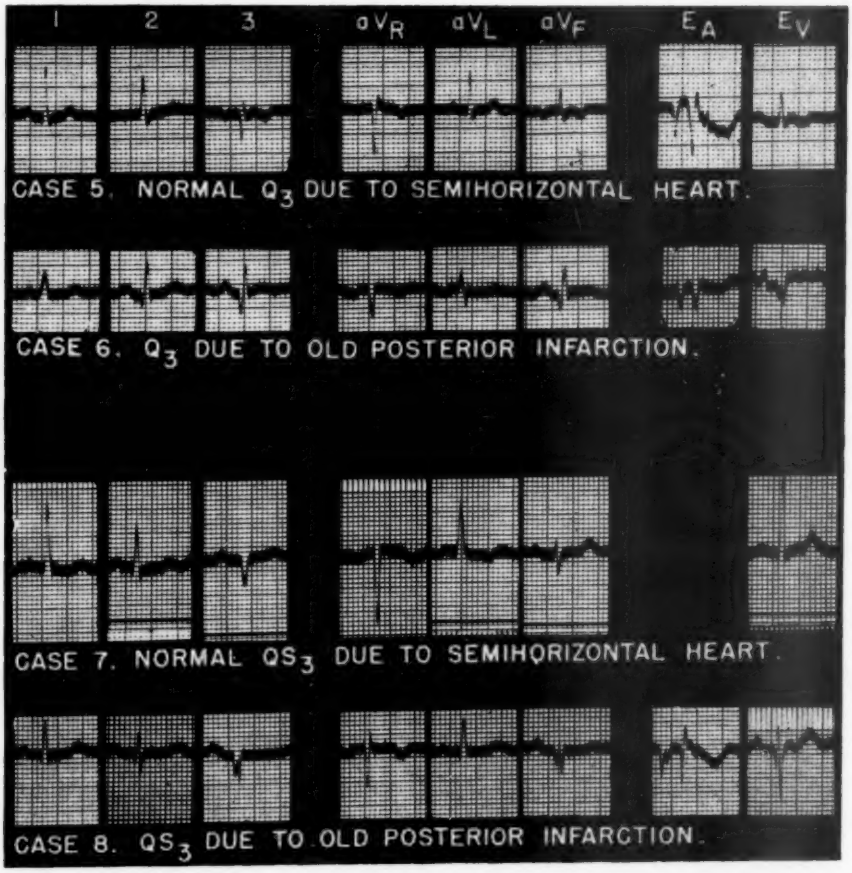


Fig. 4.—Use of augmented unipolar left leg potential (Lead aV_F) to differentiate the normal Q_3 from that due to posterior infarction.

Only nine (Cases 4, 8, 10, 13, 16, 23, 35, 47, 48) of our twenty-five patients with posterior infarction fulfilled this criterion (Table I). On the other hand, three (Cases 3, 44, 45) of the twenty-five subjects with Q_3 but without posterior infarction also met the same requirement. Each of these cases had clinical and electrocardiographic signs of left ventricular hypertrophy. However, Graybiel, et al.,[25] have demonstrated a prolonged Q_3 in apparently normal aviators.

From the foregoing it is evident that neither the depth of Q_3 in relation to the tallest R, the duration of Q_3, nor the ratio of Q_2 to R_2 is entirely dependable for determining the presence or absence of old posterior infarction.

In Figs. 3, 4, and 5, electrocardiograms of six patients with proved posterior infarction (Cases 2, 4, 6, 8, 10, and 12) are paired off for purposes of comparison with the electrocardiograms of six subjects in whom the diagnosis of posterior infarction was excluded (Cases 1, 3, 5, 7, 9, and 11). The QS_3 type of complex described by Durant[21] is represented in Cases 7 and 8; the QR complex of Pardee,[15] in the remainder. Attention is directed to the close resemblance of the standard leads of each pair of cases. Comparison of Q_3 of the even-numbered cases, in which the presence of posterior infarction was established, with the corresponding odd-numbered cases, in which it was excluded, reveals no significant difference in the duration of Q_3, in its absolute voltage, or in its amplitude relative to the tallest R in the standard leads. On the other hand, comparison of the QRS complexes in Lead aV_F of each pair of cases reveals significant differences in contour which permit a sharp differentiation between the infarcted and the control cases.

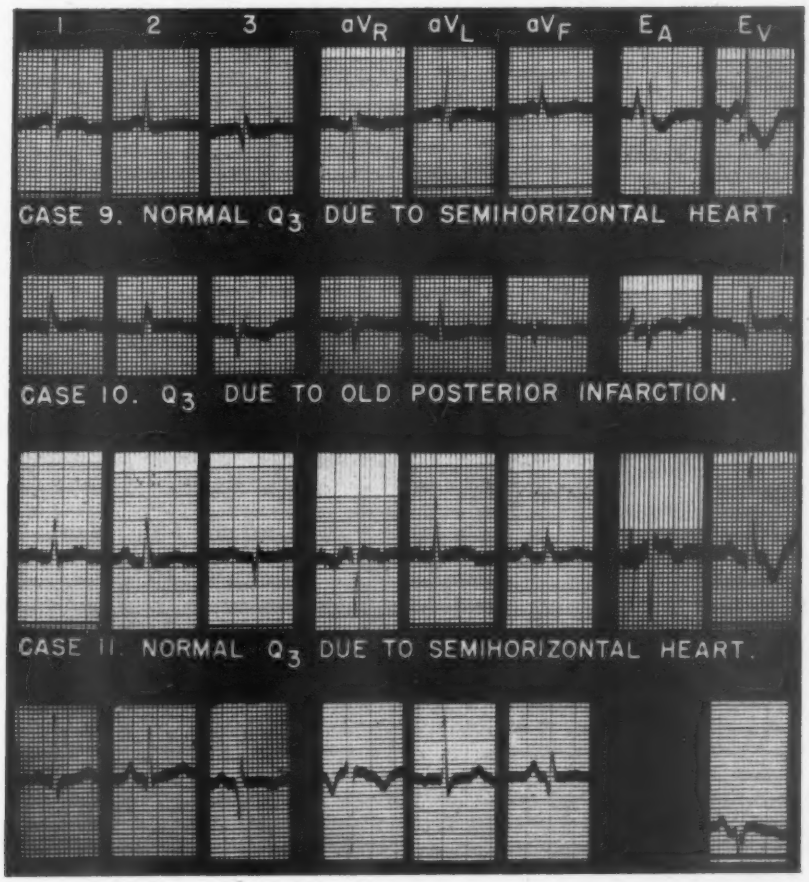


Fig. 5.—Use of augmented unipolar left leg potential (Lead aV_F) to differentiate normal Q_3 from that due to posterior infarction.

Further comparisons are afforded by Figs. 6 and 7, which illustrate cases in which the diagnosis was established by autopsy. Fig. 6 includes a classical recent posterior infarct (Case 13), a case which is less typical, partly because of low voltage (Case 14), and a control (Case 15) which had a QRS-T complex suggestive of posterior infarction in Lead III but not in Lead aV_F. From this, together with the right axis deviation in the standard leads and the inversion of the T wave in the precordial leads over the right ventricle, the correct diag-

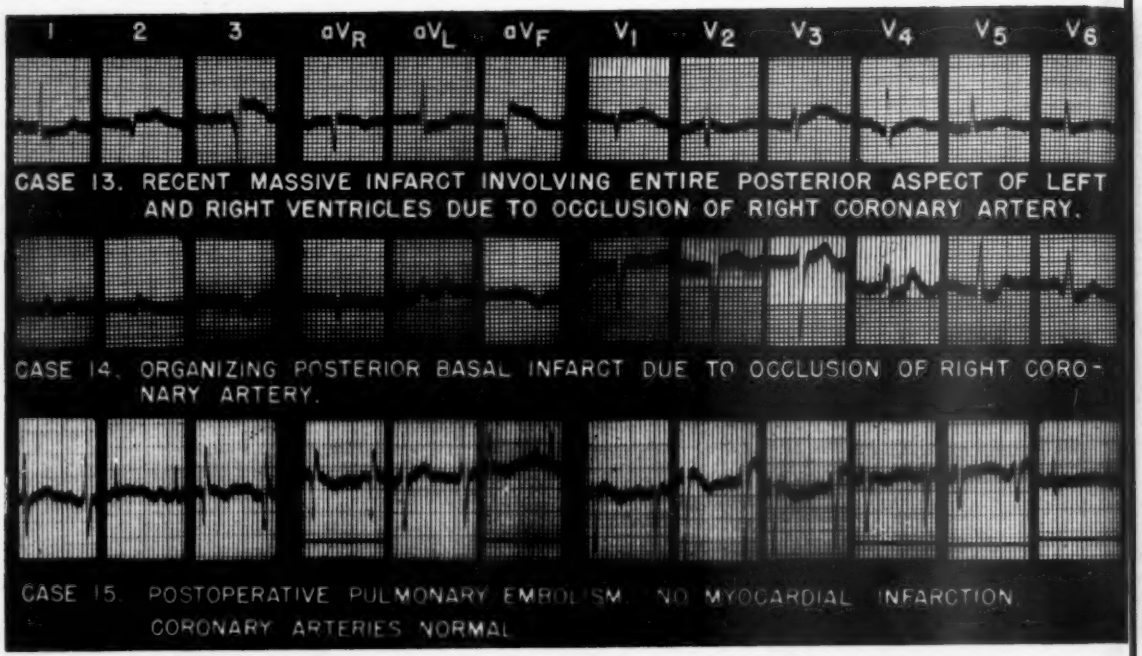


Fig. 6.—Cases with autopsy confirmation.

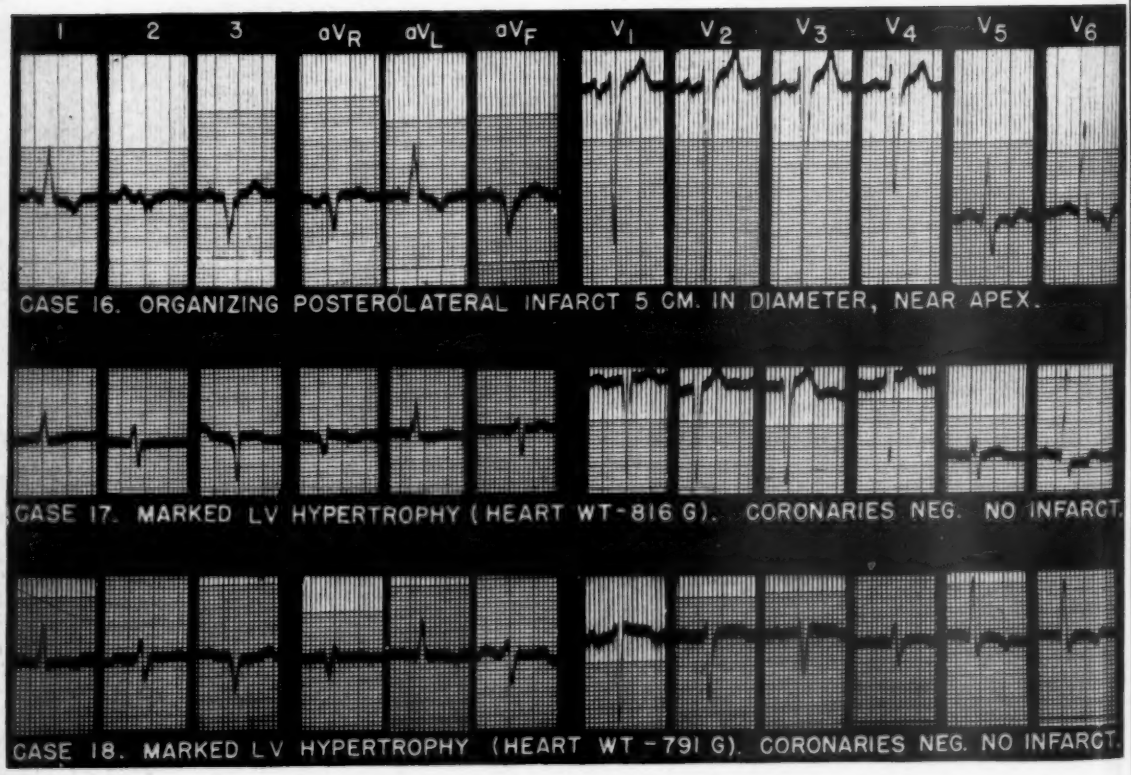


Fig. 7.—Cases with autopsy confirmation.

nosis of acute cor pulmonale was readily made electrocardiographically. Fig. 7 illustrates the appearance of a QS_3 type of complex both in patients with posterior infarction (Case 16) and in persons without infarction (Cases 17 and 18). Case 16 is readily differentiated from Cases 17 and 18 by the contour of the QRS in Lead aV_F but not by the contour of QRS_3.

C. *Comparison of Lead aV_F in Posterior Infarction With That in Uninfarcted Controls.*—

1. Incidence of QaV_F in the Two Groups: Since the potential of the posterior inferior surface of the left ventricle is transmitted through the diaphragm and intervening structures to the left leg, a Q wave in Lead aV_F would be expected if this aspect were infarcted. Of our twenty-four electrocardiograms of posterior infarction exhibiting a Q_3, a measurable Q wave occurred in Lead aV_F in all but two subjects (Cases 46 and 47, Fig. 8).

In both of these subjects, the acute attack had occurred approximately one year prior to this study and was established by typical serial changes in the electrocardiogram. Esophageal leads taken at the same time as Lead aV_F were typical of old posterior infarction. The presence of an abnormal Q wave in the esophageal leads and its absence in lead aV_F suggests that the infarct may have been located high on the posterior myocardial wall, near the auricular margin.

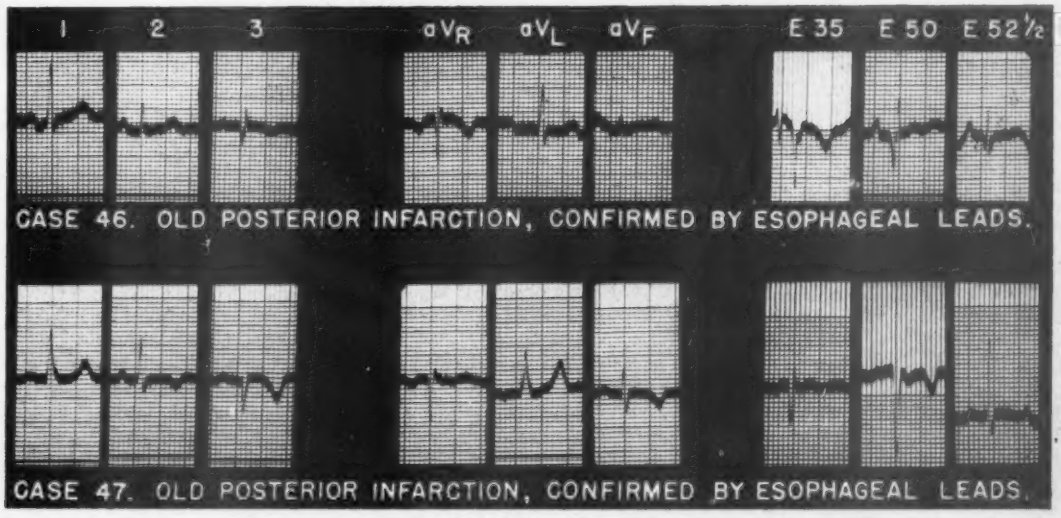


Fig. 8.—Cases in which Lead aV_F failed to reveal the presence of old posterior infarction.

This premise is supported by the fact that esophageal leads taken from a point 50 cm. from the nares were diagnostic of posterior infarction in Case 47, whereas leads taken at 52.5 cm. and below were normal. In Case 46 signs of posterior infarction were unmistakable at 50 cm. but had almost disappeared at 52.5 centimeters. Unfortunately no tracings were obtained at lower levels in this patient. If an infarct near the auriculoventricular junction does not extend a sufficient distance toward the apex to reach the diaphragmatic aspect of the left ventricle, one would anticipate no changes in aV_F even though the esophageal leads are diagnostic.

In Case 50 (Fig. 9), a small R and a deep S wave were found both in Lead aV_F and in standard Lead III instead of the classical QR or QS complex. The diagnosis of posterior infarction was made by the presence of cove-shaped T waves in Leads II, III, and aV_F, and was confirmed by esophageal leads. In all

tracings, however, a small initial R wave was present.* The fact that the unipolar extremity leads showed horizontal position of the heart suggests that a portion of the right ventricle as well as the left may have been directed against the diaphragm, and therefore may have contributed to the pattern in Lead aV_F. The activation of this portion of the right ventricle may account for the small initial R wave which appeared in Lead aV_F and was carried over into Lead III.

A measurable QaV_F occurred in eight of the twenty-five persons without posterior infarction (Table II). It is therefore evident that the mere presence of a Q wave in Lead aV_F does not necessarily indicate the existence of a posterior infarct. Since all twenty-five of these control subjects had prominent Q waves in Lead III, it is obvious that QaV_F is a much less common finding than Q_3 in the absence of infarction.

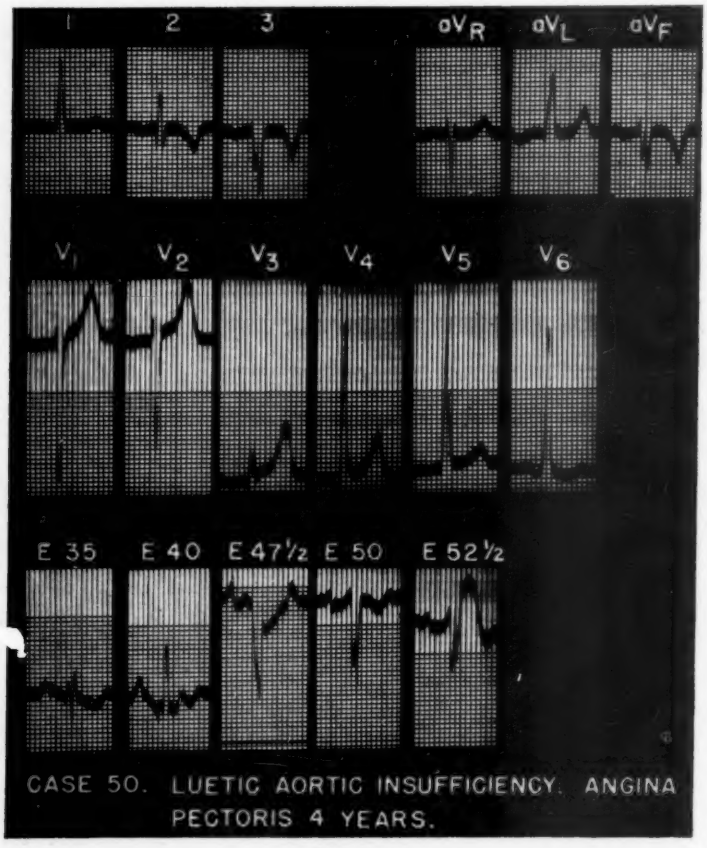


Fig. 9.—Coronary T waves in Leads II, III, aV_F, and E_V. Q waves absent.

2. Duration of QaV_F in the Two Groups: Of the twenty-two patients with infarction who showed QaV_F, this deflection was 0.04 second in duration or longer in only three instances (Cases 10, 16, and 48). In none of the uninfarcted controls did the QaV_F reach 0.04 second. Thus a QaV_F that is 0.04 second or more in duration is suggestive of posterior infarct, but is of rare occurrence.

3. Voltage of QaV_F in the Two Groups: In the twenty-two patients with infarct the voltage of QaV_F varied from 0.1 to 0.8 mv., while in the eight per-

*Complexes of this configuration are sometimes erroneously classed as Q waves. The presence of a definite antecedent R, even though small, indicates that the downward deflection is, by definition, an S, not a Q wave.

sons without posterior infarct it showed a similar range. It is thus evident that a normal and abnormal QaV_F cannot be positively distinguished by the absolute voltage.

When the voltage of QaV_F is considered in relation to that of the R wave in the same lead, a sharper differentiation may be made between the two groups.

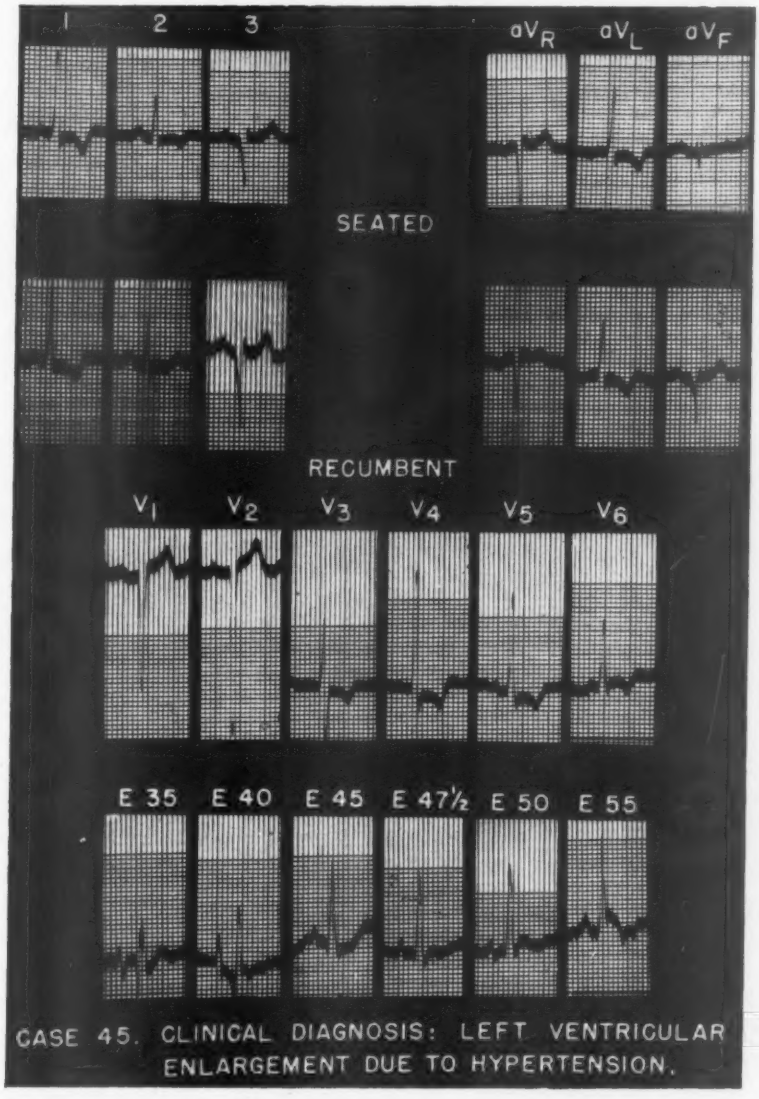


Fig. 10.—Marked postural variations in QRS in Lead aV_F. Misleading Q waves in this lead, taken in the recumbent position.

In the twenty-two tracings from patients with posterior infarction showing a Q deflection in Lead aV_F, the amplitude of the Q was more than 25 per cent of the succeeding R in every instance. On the other hand, a QaV_F which was more than 25 per cent of RaV_F was found in only three of the twenty-five persons without infarction (Cases 26, 29, and 45).

In two of these three persons (Cases 26 and 29), QaV_F was very small (measuring 0.13 and 0.2 mv., respectively) and was followed by R waves which were also of low voltage. It is doubtful if much significance can be attached to Lead aV_F when the voltage is so small.

A deep QaV_F followed by a small R wave, resembling the pattern in posterior infarction, was found in only one of the twenty-five subjects in whom posterior infarction had been excluded by history and esophageal leads (Case 45, Fig. 10). In this patient, there was clinical and electrocardiographic evidence of left ventricular hypertrophy. It is noteworthy that QaV_F was present only when the patient was in the recumbent posture, and disappeared completely when the patient was seated. Since Lead aV_F in the recumbent posture closely resembled V_1 and V_2, whereas Lead aV_L resembled Leads V_5 and V_6, it is evident that the heart was in the horizontal position, and the right ventricular potentials were transmitted to the diaphragm and left leg and the left ventricular potentials to the left arm. Thus the Q wave in Lead aV_F is analogous to that commonly observed in precordial leads over the right ventricle in patients with left ventricular hypertrophy. When the patient assumed the sitting posture, the lowering of the diaphragm probably caused sufficient rotation so that left ventricular potentials were directed, in part, toward the left leg, resulting in a small RSR complex. The reason for the deep Q_3 in the sitting, as well as in the recumbent, posture will be considered in the discussion.

Lead aV_F was misleading, then, in one of the persons without posterior infarction (Case 45, Fig. 10) and in two of the patients with infarction (Cases 46 and 47, Fig. 8). Although, on the whole, Lead aV_F proved more reliable than standard Leads II and III in the diagnosis of posterior infarction, these exceptions emphasize the fact the Lead aV_F is not infallible for this purpose. The information it supplies must be correlated with other electrocardiographic and clinical data to minimize error.

D. *Postural Variations of Q_3 and QaV_F.*—Standard and augmented unipolar extremity potentials were taken in the sitting and recumbent postures in eight persons in whom infarct was excluded and in one patient with posterior infarction. Q_3 was significantly deeper in the seated, than in the recumbent, posture in five of the eight uninfarcted controls, whereas the reverse was true in two subjects, and no difference was noted in one. A QaV_F was present in the recumbent, but absent in the seated, posture in one patient (Case 45, Fig. 10) whom we have already discussed. A very small QaV_F was present in the seated posture in one patient but absent in recumbency. The remaining six patients showed no Q wave in aV_F taken in either posture.

The subject with posterior infarction (Case 35) showed an abnormal Q wave in Leads III and aV_F in both postures, but significantly deeper in the recumbent, than in the seated, posture. It is thus evident that the presence of postural variations in the depth of Q_3 or QaV_F should not in itself be construed as evidence against the presence of an infarct.

COMMENT

1. *The Derivation of Lead III.*—The mechanism whereby the Q deflection is produced in Lead III is made clearer from an understanding of the derivation of that lead. The unipolar extremity leads are always taken with the exploring electrode connected to the positive terminal of the galvanometer and with an indifferent electrode of zero potential connected to the negative terminal. Thus a positive potential in the extremity connected with the exploring electrode is recorded as an upright deflection, a negative potential as a downward deflection. On the other hand, the standard leads are bipolar leads, each representing the fusion of the unipolar leads, which contribute equally but in opposite directions to the deflections of the galvanometer. Using Einthoven's equation, Lead III =

Lead II – Lead I, Wilson, MacLeod, and Barker[39] demonstrated that Leads I, II, and III could be calculated mathematically from known unipolar extremity potentials from the right arm, left arm, and left leg (V_R, V_L, and V_F, respectively). By transposing these values into Einthoven's equation, they showed that Lead I must equal $V_L - V_R$; Lead II, $V_F - V_R$; and Lead III, $V_F - V_L$. Thus in taking Lead III, the left leg is connected to the galvanometer in the same manner as in taking the unipolar left leg lead, whereas the left arm is connected in the opposite manner, i.e., to the negative instead of to the positive pole. Hence, Lead III is derived either by subtracting V_L from V_F or by adding the mirror image of V_L to V_F.

Goldberger's[33, 34] augmented unipolar extremity potentials may be used in these same equations if the result is multiplied by two-thirds, since the deflections obtained when his indifferent electrode is used amount to one and one-half times the actual potentials in the extremities.

Thus:

$$\text{Lead I} = (aV_L - aV_R) \times 2/3,$$
$$\text{Lead II} = (aV_F - aV_R) \times 2/3,$$
$$\text{and Lead III} = (aV_F - aV_L) \times 2/3.$$

2. *The Derivation of Q_3 and QaV_F in Posterior Infarction.*—Wilson's[27] explanation of the origin of the Q wave in myocardial infarction is generally accepted and has been summarized in the introduction. Kossmann and de la Chapelle[43] have applied Wilson's concept to an explanation of the derivation of the Q wave in Leads II, III, and V_F in cases of posterior infarction. Fig. 11 represents this diagrammatically.

When an exploring electrode is applied to an extremity and an indifferent electrode of zero potential is used, the galvanometer of the electrocardiograph records potential variations in the extremity. The potential variations in the left leg are governed principally by those at the epicardial surface which customarily faces toward the left leg, namely, the epicardial surface of the postero-inferior (diaphragmatic) aspect of the left ventricle. While this portion of the ventricle is being activated in the normal heart by the passage of an impulse from the endocardial to the epicardial surface, the latter surface, as well as the left leg, is electro positive, resulting in the registration of an R wave in Lead aV_F.

If the postero-inferior aspect of the left ventricle is completely infarcted, an impulse no longer passes through this portion of the ventricular wall. Thus, the epicardial surface reflects the potential variations of the cavity of the left ventricle. The ventricular cavity is electronegative while the impulse is passing from endocardium to epicardium in the uninfarcted portions of its walls. This electronegativity is reflected through the infarcted diaphragmatic wall to the left leg and is registered as a Q wave in Lead aV_F.

Since Lead aV_F is one of the two unipolar leads composing the bipolar standard Lead III, its Q wave contributes to the depth of Q_3. In addition, the unopposed, upwardly directed impulses in the uninjured anterosuperior wall (Fig. 11) of the left ventricle cause marked electropositivity at the epicardial surface directed toward the left arm, which is recorded in the unipolar lead from that extremity as a tall R wave. From the arithmetical derivation of Lead III, this contributes even more depth to the Q deflection in that lead.

3. *The Derivation of Q_3 in Semihorizontal or Horizontal Hearts.*—Just as the unipolar lead of the left leg reflects the potential at the epicardial surface of that portion of the heart which faces toward the left leg, the unipolar left arm

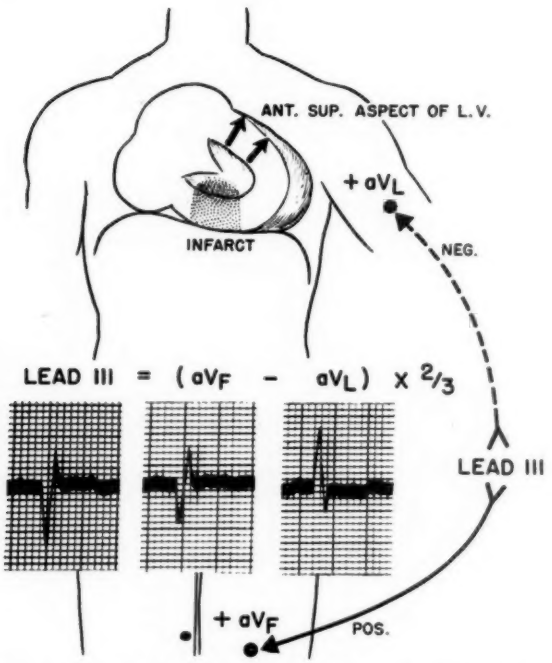


Fig. 11.—Abnormal Q waves in Leads III and aVF due to infarction of the posterior diaphragmatic aspect of the left ventricle.

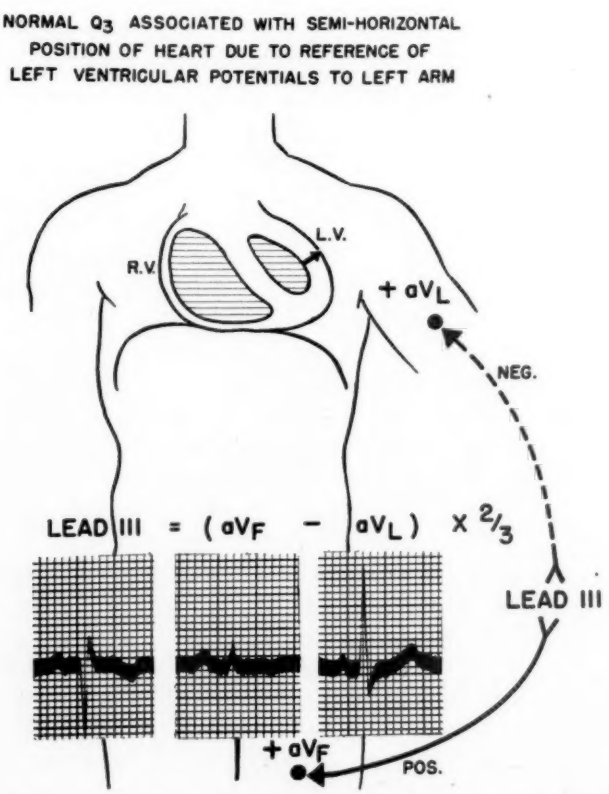


Fig. 12.—Normal Q_3 associated with semihorizontal position of the heart due to reference of left ventricular potentials to left arm.

lead (aV_L) is governed chiefly by the potential at the epicardial surface which faces toward the left arm (Wilson, et al.[37, 39]). When the heart is in the horizontal or semihorizontal position, the lateral and apical portions of the left ventricle face toward the left arm (Fig. 12); impulses passing from endocardium to epicardium in this portion of the wall during the activation of the ventricle result in electropositivity at the epicardial surface, which is represented as a tall R wave in Lead aV_L.

At the same time, the right ventricular surface of the horizontal or semihorizontal heart has been rotated to face more toward the left leg. Lead aV_F will resemble precordial Leads V_1 and V_2 if the right ventricular potentials are referred to the diaphragm (horizontal position), whereas it will be of very low voltage if a portion of the left as well as the right ventricle form the diaphragmatic surface of heart (semihorizontal position). Fig. 12 illustrates the production of a Q wave in the bipolar standard Lead III through the fusion of the unipolar leads from the left leg and left arm. Subtracting the tall left ventricular R wave of Lead aV_L from the small, upright or diphasic deflection of Lead aV_F will account for the deep downward deflection in standard Lead III, which, in some cases, may be an S wave, but in others may be a Q or QS wave as deep as any found in posterior infarction. This is a not an infrequent occurrence in persons with normal hearts which are semihorizontal in the electrical position. If left ventricular hypertrophy is present, Q_3 so produced may not only be deep, but also prolonged to 0.04 second or more.

As might be expected, the Q wave of horizontal or semihorizontal hearts is found only in Lead III, but not in Lead II, which is composed of the left leg and right arm potentials. The tall R wave of the left arm lead, which is the source of Q_3 in hearts which are in this position, is not represented at all in Lead II.

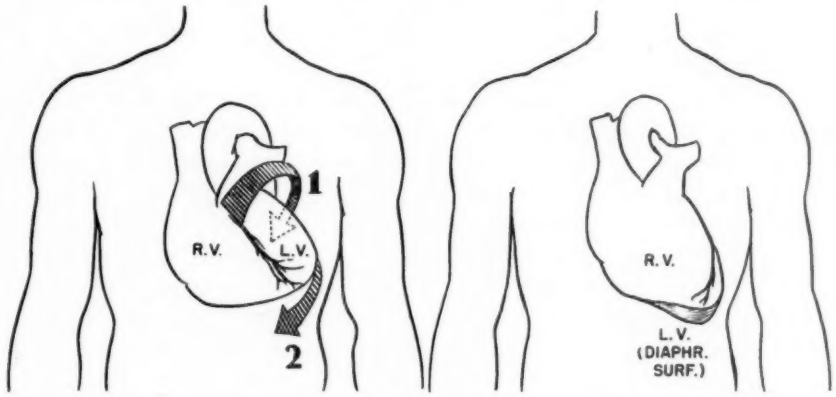
The six paired electrocardiograms in Figs. 3, 4, and 5 have already been mentioned. We return to these curves to re-emphasize the similarity of the standard leads in each pair. However, by reference to Lead aV_F, a clear-cut differentiation may be made between patients with posterior infarction and normal subjects.

4. *The Derivation of Q_3 in Vertical Hearts.*—In studying the effect on the electrocardiogram of positional changes in the dog's heart, Meek and Wilson[40] found that when the apex was moved to the right on an axis extending anteroposteriorly through the body, curves characteristic of right axis deviation were obtained. Similar curves were produced with rotation of the heart on *its own* longitudinal axis, so that the front of the heart was turned more to face the left. These two types of rotation are represented diagrammatically in Fig. 13. Experimentally, in the dog, the rotation could be limited to one or the other of two axes, but combined rotation on both axes was found to occur when the heart was displaced to one side.

An interesting study of rotation of the human heart was done by Kountz, Prinzmetal, Pearson, and Koenig.[41] By perfusion of the heart immediately after death, they were able to reactivate it and to obtain reasonably normal electrocardiograms. Curves typical of right axis deviation were obtained when the heart was rotated clockwise on its own axis (Fig. 13, arrow *1*), whereas the reverse was true upon counterclockwise rotation. Elevation of the diaphragm, whether due to deep expiration, recumbent posture, or obesity, may be associated with a horizontal or semihorizontal heart (Fig. 13, *a*). On the other hand, the lower position of the diaphragm due to deep inspiration, erect posture, pul-

monary emphysema, or an elongated, asthenic chest wall, is more often associated with vertical position of the heart (Fig. 13, *b*).

Lewis[11] stated that a Q deflection was the first evidence of ventricular activation and represented the passage of an impulse through the ventricular



a. EXPIRATORY POSITION OF HEART. ARROWS SHOW SUBSEQUENT ROTATION 1 UPON HEART'S OWN LONGITUDINAL AXIS AND 2 UPON ANTEROPOSTERIOR AXIS.

b. INSPIRATORY POSITION OF HEART AFTER COMPLETION OF ROTATIONS DESCRIBED IN a.

Fig. 13.—Changes in position of heart with respiration or posture.

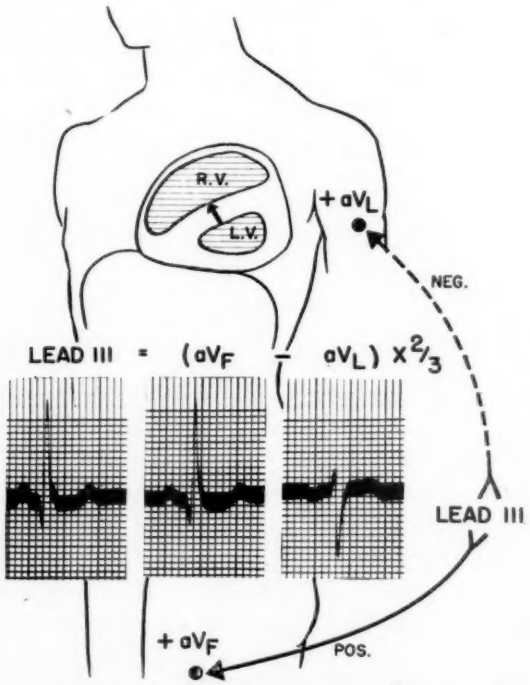


Fig. 14.—Normal Q_3 and QaV_F associated with ventrical position of the heart due to activation of the left ventricular half of the septum.

septum. Mahaim[42] found that the first offshoots from the left bundle branch into the left half of the septum occurred at a point much nearer the bifurcation of the bundle of His than the first offshoots from the right bundle branch into the right half of the septum. From this he concluded that the anterobasal

aspect of the left side of the interventricular septum was the first portion of the ventricle to be activated, and it gave rise to the very beginning of the QRS deflection.

Septal activation not only is initiated on the left side, but also preponderates on that side due to the fact that the left ventricular portion of the septum is thicker than the right. Thus, the resultant electrical vector can be represented by an arrow (Fig. 14) passing from the left ventricular cavity toward the right.

In the vertical position (Fig. 13, *b*) combined rotation of the heart upon an anteroposterior axis extending through the body (Fig. 13, *a;* arrow *1*) and upon its own longitudinal axis (Fig. 13, *a;* arrow *2*) causes the right ventricle to lie anterosuperiorly and the left, postero-inferiorly. Fig. 14 is a diagram of an oblique section through such a vertical heart, to show the relation of the septum to the ventricular cavities. The arrow in Fig. 14 represents the vector associated with activation of the septum. Since the right ventricle lies above and in front of the left in the vertical heart, this arrow must be directed upward, giving rise to a Q wave in Lead aV_F which is carried over into standard Leads II and III.

The septal Q wave is of very brief duration, since the electrical changes in the rest of the myocardial wall rapidly take ascendency. This septal Q wave is followed by a relatively tall R wave due to activation of that portion of the left ventricle which lies opposite the septum. When the heart is vertically placed, the major portion of the left ventricle is directed toward the diaphragm, giving rise to the tall R in Leads aV_F, II, and III, which follows the relatively small septal Q wave. The Q/R ratio is well below the limit of 25 per cent.

SUMMARY

An attempt was made to evaluate the diagnostic significance of the QRS pattern in the augmented, unipolar left leg lead (Lead aV_F) as a means of establishing or excluding the diagnosis of posterior infarction. Forty-nine patients were selected for study because of the presence of a prominent Q wave in standard Lead III. One additional patient with posterior infarction was included. This patient did not have Q waves but exhibited the classical ST-T wave changes in Lead III.

Multiple precordial and unipolar extremity leads were taken on every subject and esophageal leads were taken on forty-four of the fifty subjects. The presence of a posterior infarct was established in a total of twenty-five subjects, in four of these by autopsy, and in the remaining twenty-one by typical esophageal leads. The infarct was months or years old in all but four cases. Posterior infarction was excluded in a total of twenty-five subjects, in three by autopsy and in the remaining twenty-two by negative esophageal leads.

In all cases where posterior infarction was excluded, a prominent Q_3 or QS_3 was present. This amounted to 25 per cent or more of the tallest R in twenty-three of the twenty-five cases; from an examination of the standard leads alone, many of these cases could not be distinguished from cases proved to have old posterior infarction. The pattern of the QRS in Lead aV_F proved to be of considerable help in this differentiation.

A QaV_F which was 25 per cent or more of RaV_F was found in twenty-two of the twenty-five subjects proved to have posterior infarct, and in only three of the twenty-five subjects in whom the diagnosis of posterior infarction had been excluded. In both cases of posterior infarct which had a Q_3 but failed to show

QaV_F, esophageal leads suggested that the infarct was located high on the posterior wall, near the auricular margin. The voltage of the QRS wave in Lead aV_F was low in two of the three uninfarcted controls which showed a Q/R ratio exceeding 25 per cent in this lead. In the remaining case, the deep Q wave was present in Lead aV_F when the patient was recumbent, but disappeared when the curve was taken with the patient in the erect posture.

The mechanism of production of the Q wave in standard Lead III has been discussed separately for (a) that associated with posterior myocardial infarction, (b) that occurring in uninfarcted hearts with a horizontal or semihorizontal electrical axis, and (c) that occurring in uninfarcted hearts with a vertical electrical axis.

CONCLUSIONS

1. The contour of the QRS complex in the augmented unipolar left leg lead (Lead aV_F) is of considerable value in the differentiation of the normal from the abnormal Q wave in standard Lead III.

2. The presence of a Q wave in Lead aV_F which is more than 25 per cent of the voltage of the R wave in the same lead constitutes strong but not absolutely pathognomonic evidence for the existence of a posterior myocardial infarct.

3. The absence of a QaV_F or the presence of an insignificant deflection which is less than 25 per cent of the subsequent R wave constitutes strong but not absolutely conclusive evidence against the presence of a posterior myocardial infarct.

We wish to express our appreciation of the work of Miss Evelyn Erickson, Miss Geraldine Chesney, and Mr. Clayton Oliver in preparing the illustrations.

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DELAYED CONDUCTION IN THE BUNDLE BRANCHES

A Report of Two Cases in Which the P-R Interval Increased With Changes From Left to Right Bundle Branch Block

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THE occurrence of incomplete or partial* bundle branch block has been postulated on theoretical grounds[1] in analogy to the disturbances of conduction which result from lesions of the main stem of the bundle of His. In animal experiments various kinds of partial block in the bundle branches have been produced.[1-4] The clinical diagnosis of incomplete bundle branch block, however, meets with considerable difficulties. This is in part due to the fact that the transmission of impulses in the bundle branches is included in the auriculoventricular conduction time. Therefore, a disturbance of conduction which involves equally both bundle branches produces electrocardiographic changes indistinguishable from those caused by lesions of the main stem of the bundle. Interruption of conduction in both bundle branches brings on complete auriculoventricular dissociation. Or, if there is an equal delay of conduction in both bundle branches, it is added to the auriculoventricular conduction time causing prolongation of the P-R interval. If, on the other hand, the delay of conduction is unequal in the two branches or affects one bundle branch only, asynchronous activation of the ventricles results, causing widening of QRS. In those cases where the delay of conduction in one bundle branch is longer than the time required for the excitation transmitted through the other branch to reach the affected ventricle by way of the interventricular septum, the resulting widening and deformation of QRS is the same as that caused by complete bundle branch block.[3] In the dog, for instance, a delay of conduction in one bundle branch measuring 0.04 second or more cannot be differentiated in the electrocardiogram from complete interruption of conduction produced by cutting the bundle branch. If the delay of conduction is less than 0.04 second aberrations of the ventricular complexes of variable degree are observed similar to those which result from combining the levocardiogram and the dextrocardiogram in variable time relations.[3]

It is, therefore, understandable that the clinical diagnosis of incomplete bundle branch block is based more often on conjecture than on unquestionable evidence. It has been suggested that bundle branch block which is but temporary is due to delay rather than interruption of conduction.[1] Also, the occurrence, both in the experimental animal[1-3] and clinically,[5, 6] of gradual transition of aberrant ventricular complexes which are characteristic of bundle branch block into normal complexes, has been explained by gradual increase in the conductive capacity of a bundle branch in the presence of incomplete bundle branch block. Precordial leads occasionally reveal right bundle branch block, although the duration of QRS is not more than 0.1 second. Such disturbance has been interpreted as due to incomplete bundle

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*The terms "incomplete" and "partial" bundle branch block are used here synonymously to denote either delayed or intermittent conduction in the bundle branches as opposed to complete interruption of conduction.

branch block.[7] Furthermore, cases are on record in which normal ventricular complexes alternate regularly with grossly aberrant forms suggesting the presence of partial bundle branch block with a conduction ratio of 2:1, 3:1, or 4:1.[5, 8-11] These observations present the most obvious instances of partial block in the bundle branches. Far more difficult, for reasons which have been discussed, is the diagnosis of a simple delay of intraventricular conduction in one bundle branch. Such disturbances may be disguised as complete bundle branch block,[3] if the other bundle branch has preserved its conductive capacity; or as prolonged auriculoventricular conduction time, if the second bundle branch fails to conduct properly. In the experimental animal it is possible by cutting one bundle branch and injuring the other to produce, in addition to aberrant ventricular complexes characteristic of block of the severed bundle branch, either prolongation of the P-R interval or dropped ventricular beats. Conditions as favorable for the analysis of intraventricular conduction disturbances are rarely met in clinical instances. We have observed two cases in which alternation of right and left bundle branch block provides what seems to be stringent evidence of delayed conduction in a bundle branch. These cases are the object of this report.

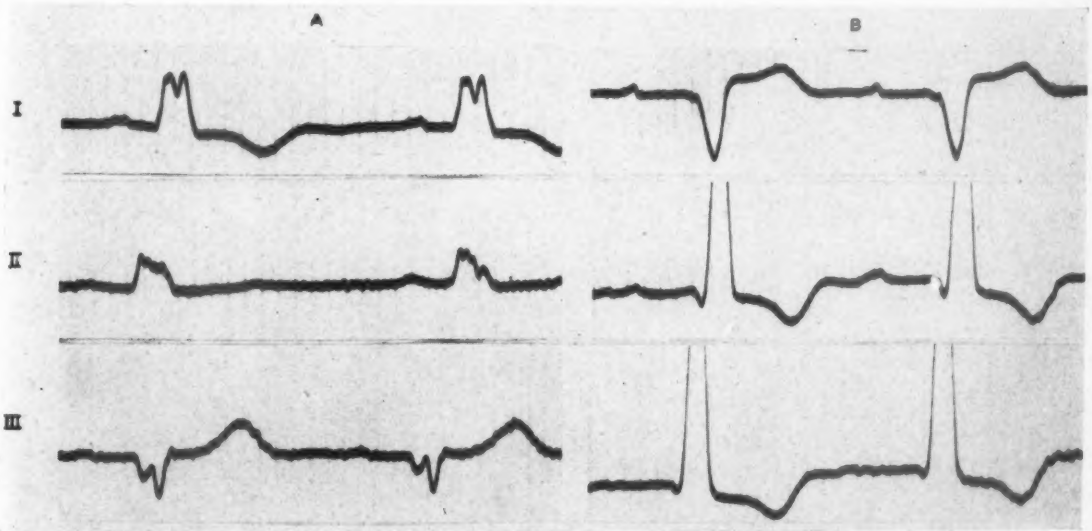

Fig 1.—Case 1. Two types of ventricular complexes are noted; in both the duration of QRS is 0.12 to 0.13 second. One type (*A*) shows an upward directed main deflection in Lead I, suggestive of left bundle branch block. Its P-R interval is 0.17 second. The other type (*B*) presents a downward directed main deflection in Lead I, indicative of right bundle branch block. Its P-R interval is 0.23 second. (Time intervals equal 0.05 second.)

CASE REPORTS

CASE 1.—K. W., a white woman, aged 76 years, had suffered an attack of protracted severe pain across the chest six weeks prior to examination. The pain was associated with cold sweat. Since then, when walking, the patient had experienced pressure in the chest which forced her to stop for a while. Physical examination revealed a blood pressure of 130/60 mm. of mercury. A broad, heaving apical thrust was noted; this pointed, in the absence of significant murmurs, to previous hypertension. Fluoroscopy showed distinct enlargement of the heart to the left and deposits of lime salt in the aorta.

The electrocardiogram (Fig. 1) revealed sinus arrhythmia with an average rate of 88 per minute. Two types of ventricular beats were noted; both had deformed complexes, and the duration of QRS measured about 0.13 second. One type showed upright initial deflections in Lead I (Fig. 1, *A*) suggesting the presence of left bundle branch block. The other type presented a downward directed QRS in Lead I (Fig. 1, *B*) pointing to a lesion

in the right bundle division. Right and left bundle branch complexes alternated in the same tracing (Fig. 2) without showing any constant relation to the variable length of the sinus period. The most striking feature was a prolongation of the P-R interval which accompanied every change from left to right bundle branch block. Those complexes presenting the features of left bundle branch block had a P-R interval of 0.18 second, whereas the beats with the characteristics of right bundle branch block showed a P-R interval measuring, on the average, 0.23 second.

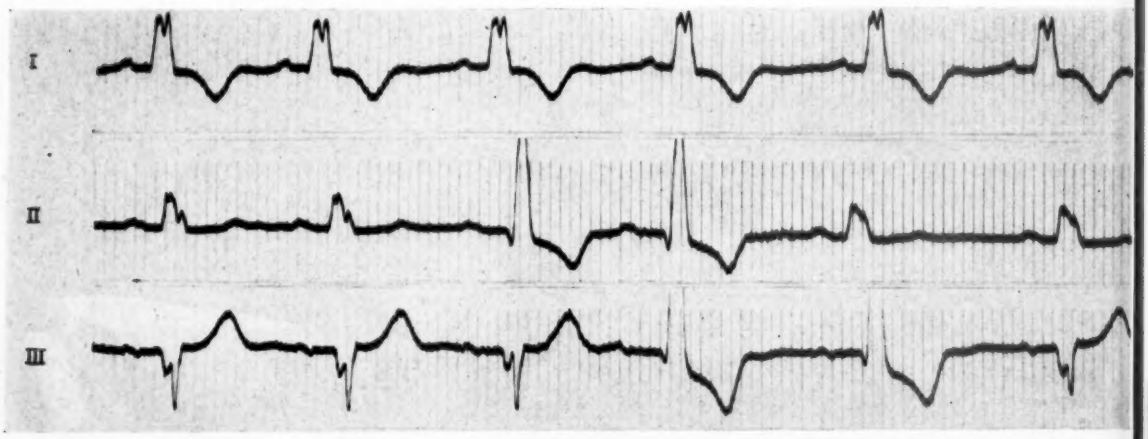

Fig. 2.—Case 1. The same two types of ventricular complexes are noted as in Fig. 1, but they alternate in irregular intervals. Most of the beats belong to the type which is characterized by upward QRS in Lead I, suggestive of left bundle branch block. Their P-R interval is 0.18 second. The second type is seen in Leads II and III only; it is characterized by deep Q waves and high R waves, suggestive of right bundle branch block. The P-R interval of these beats is 0.23 second. (Time intervals equal 0.05 second.)

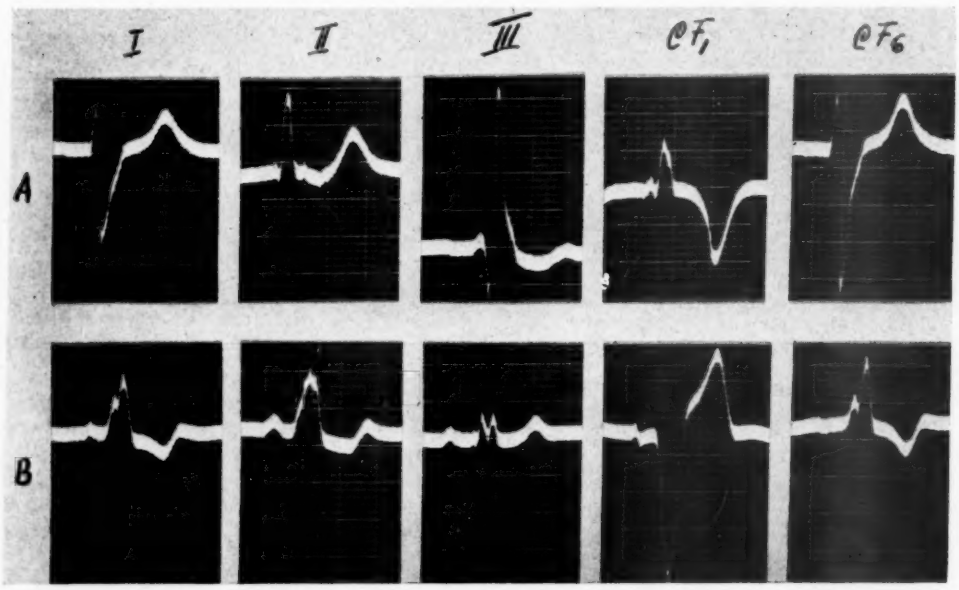

Fig. 3.—Case 2. Two types of ventricular complexes are noted. In both the duration of QRS is 0.16 second. One type (*A*) shows a prominent broad S wave in Lead I, suggestive of right bundle branch block. In Lead CF_1, the QRS complex is upright and bifid; in Lead CF_6 a prominent broad S wave is noted.

Tracing *B* presents the other type of ventricular beats which is characterized by upright QRS complexes in the limb leads. In Lead CF_1 there is a broad QS wave; in Lead CF_6 the QRS complex is upright, broad, and notched. These are the features of left bundle branch block.

Case 2.—M. Y., a white man, aged 51 years, had always been well and had never complained of his heart. Four weeks prior to admission to the hospital he suffered syncope which lasted for a few minutes. A similar attack occurred a week later. A day prior to

admission the patient experienced a number of dizzy spells. On the day of admission he had several attacks of syncope with convulsions. Physical examination revealed distant heart sounds and bradycardia with arrhythmia; the cardiac rate varied from 38 to 60 beats per minute.

Various electrocardiograms were taken which revealed the presence of partial A-V block with dropped beats. Two types of ventricular complexes were observed (Fig. 3). One (*A*) presented the features of right bundle branch block; the other (*B*) showed the characteristics of left bundle branch block.

In an electrocardiogram that was taken on March 31, 1944, both types of ventricular beats were present (Fig. 4). The tracing showed a regular sinus rhythm with a rate of 75 per minute. The P waves, with few exceptions, were followed by ventricular beats which, apparently, were conducted from the auricles. The beats which were suggestive of left bundle branch block presented upright QRS deflections in all leads. The other type, suggestive of right bundle branch block, showed prominent broad S waves in Lead I and deep Q waves and high R waves in Leads II and III. The two types of ventricular complexes alternated in varying intervals, and the changes from left to right bundle branch block were invariably accompanied by a prolongation of the P-R interval. Those beats indicative of left bundle branch block had a P-R interval of 0.16 second, while the other complexes which displayed the features of right bundle branch block were preceded by P waves in an interval of 0.21 second. The latter complexes were occasionally followed by auricular waves which were not conducted to the ventricle (Fig. 4, Lead I).

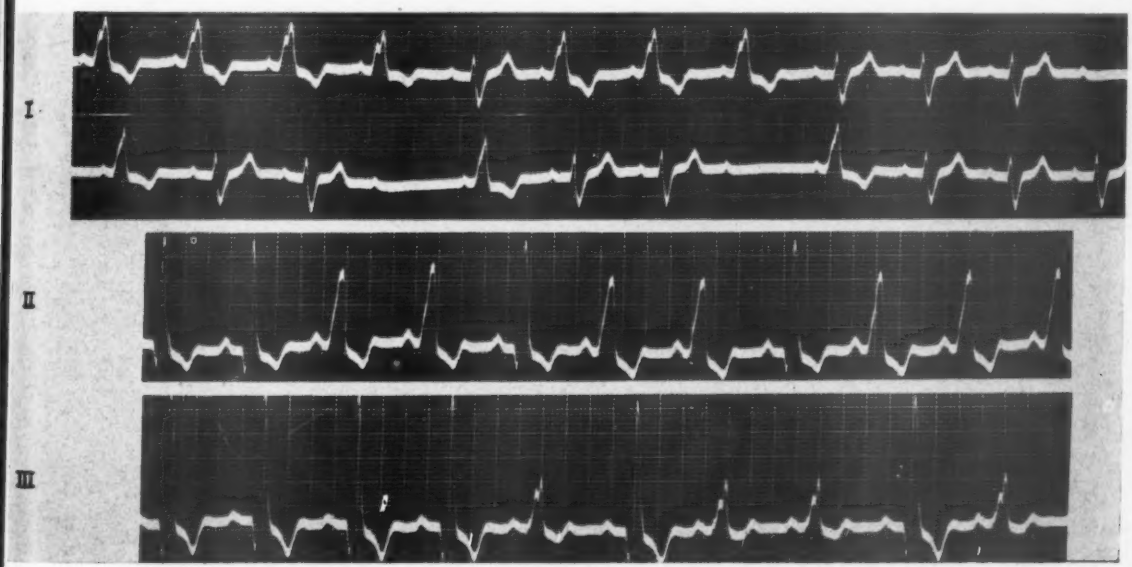

Fig. 4.—Case 2. There is a fairly regular sinus rhythm with two types of ventricular complexes similar to those seen in Fig. 3. In both the duration of QRS is 0.16 second. One type is characterized by an upward directed QRS in all leads suggestive of left bundle branch block. Its P-R interval is 0.16 second. Another type of beats presents deep wide S waves in Lead I, and marked Q waves and high R waves in Leads II and III. These beats seem to indicate right bundle branch block. Their P-R interval is 0.21 second. Most of the auricular waves are followed by ventricular complexes. Only in Lead I some of the ventricular complexes which present deep S deflections are followed by blocked P waves. (Two strips of a continuous tracing are shown in Lead I.)

COMMENT

The two cases reported here present in the electrocardiogram changes which suggest lesions in both bundle branches. Left and right bundle branch block complexes alternate in irregular sequence, but changes from left to right bundle branch block are invariably accompanied by prolongation of the P-R interval; the increase was at least 0.05 second. This feature affords a clue for the analysis of the conduction disturbance in the left bundle branch. It suggests that the left division of the bundle requires 0.05 second more than the right bundle branch to pass the stimulus to the ventricle. Because of this

delay the stimulus transmitted by the right bundle branch is able to reach the left ventricle and to activate both chambers. The resulting ventricular complexes show the features characteristic of complete left bundle branch block. At times, however, when the right bundle branch fails to transmit the excitation in due time (because of either interruption or marked delay of its conduction), the left division of the bundle activates not only the left but also the right ventricle. Its conduction delay is then added to the A-V conduction time, and the ventricular complexes which present the features of right bundle branch block have a P-R interval which is prolonged by 0.05 second.

It is conceivable that the occasional occurrence of dropped ventricular beats in Case 2 was due to further impairment of the conduction in the bundle branches. Similar conduction disturbances have been produced in the experimental animal by cutting one bundle branch and exerting pressure on the other branch.[3, 4] However, the available evidence in our case does not allow us to decide whether the periods of ventricular standstill were caused by the lesions in the bundle branches or by a concomitant obstruction in the path of the main stem of the bundle of His.

The occurrence of bilateral bundle branch block has been occasionally recorded in clinical instances.[12, 13] In fact, it might be expected even more frequently than is suggested by the few cases on record, for anatomic studies have shown that what is usually diagnosed as unilateral bundle branch block is commonly associated with bilateral lesions.[14] One of the cases reported in the literature[12] bore striking resemblance to our Case 2 but was given a different interpretation.

SUMMARY

Two cases are reported which, in the electrocardiogram, presented aberrations of the ventricular complexes of two types, suggestive of alternation of right and left bundle branch block. Changes from left to right bundle branch block were invariably accompanied by prolongation of the P-R interval; the increase measured 0.05 second or more. This fact suggested that what first appeared to be complete left bundle branch block was actually a delay of conduction in the left division of the bundle measuring 0.05 second. The delay in the left branch allowed the excitation, passed by the right bundle branch, to reach the left ventricle and to activate both chambers. At times, however, when the conduction in the right bundle branch failed, the left branch of the bundle took over the task of activating not only the left but also the right chamber. The delay of its conduction was then added to the A-V conduction time, causing a prolongation of the P-R interval by 0.05 second.

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A SIMPLE SWITCHING DEVICE TO FACILITATE THE RECORDING OF ELECTROCARDIOGRAMS EMBODYING MULTIPLE TYPES OF LEADS

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SINCE 1932,[1, 2] precordial types of leads have been widely used and accepted in electrocardiography as of definite value to complement the three limb leads of Einthoven for practical clinical purposes. During this interval, however, a considerable diversity of opinion has developed concerning the "best" location for the distant electrode and the number of chest positions that must be explored[3-5] in order to derive from precordial leads, as conveniently as possible under ordinary clinical circumstances, the most reliable and truly practical information they afford. Additional leads of special types[6-8] have also been introduced to complement or to substitute for the three limb leads for clinical purposes, but these special leads have not yet been extensively explored as regards their practical merits or reliability. It happens, therefore, that various combinations of the three limb leads with different types and numbers of precordial leads, and sometimes with other special leads, are now being employed routinely or otherwise in clinical electrocardiography, and that controversy and uncertainty exist regarding the relative virtues of these various combinations. Because of these developments, it now seems evident that many additional experimental and clinical studies will need to be contributed on the problem of electrocardiograms embodying multiple types of leads, before any satisfactory standardization of their techniques and interpretations for practical clinical use can be finally accomplished. Moreover, in consideration of the more practical aspects of this problem, it seems important that attention be given to the development of simplified methods whereby electrocardiograms embodying multiple types of leads can be recorded with convenience under ordinary clinical circumstances.

In a study now being conducted, one of us[9] is attempting to find the direct comparative evaluation of electrocardiographic records which combine the three limb leads with different types and numbers of precordial leads,[3-5] and with

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unipolar limb leads,[6] as obtained on patients with various forms of cardiac disease and on control subjects. On every individual selected for that study, electrocardiograms are secured which include Leads I, II, III, and IVF, the CF, CL, CR, and V types of leads from precordial positions 1 to 6, inclusive, and the V type of unipolar limb leads. For recording these electrocardiograms, a standard electrocardiograph,* supplemented by a "Wilson central terminal,"[6]* was initially employed. However, to secure the required series of leads with such equipment, it is necessary to effect in every case numerous interchanges in the lead-wires attached to the electrodes on the patient. These manipulations of the wiring arrangements proved tedious and complicated, and recording the required electrocardiograms with such equipment was an inconvenient and time-consuming procedure. Therefore, the switching device herein described was developed in order to simplify and facilitate the recording technique for the previously mentioned study.

This switch, when employed either for investigative or for ordinary clinical purposes, has been found extremely convenient for the recording of electrocardiograms embodying multiple types of leads. Since it is believed that the practical advantages of this simple device should be made more widely available, publication of directions for its construction and use seems warranted.

MATERIALS FOR CONSTRUCTION

The materials needed for the construction of this switching device can be obtained without particular difficulty, even in these days of priorities, at regular stores dealing in standard electrical and radio parts and supplies. The total cost of the completed switch, when no labor charges for assembling are included, is approximately $10. The individual items required for the construction are:

A. Four "radio-type" rotary switch sections, each providing eight distributed switch positions and one common contact pole.†

B. One switch kit, for assembling the individual switch sections into the switch-supporting chassis.†

C. One switch bar-knob.

D. One 12-foot length of "four-way," rubber-insulated, shielded microphone cable, containing four rubber-insulated, 26-strand wires.

E. Four 4-foot lengths of pliable, rubber-insulated, 26-strand wire for constructing the lead-wires going to the electrodes on the patient.

F. One 4-way coupling connection, for insertion between the 4-wire microphone cable and the four lead-wires. This may be improvised on any suitable basis.

G. Four "radio-type" terminal plugs (or alligator clips, if preferred) for attaching the individual lead-wires to the electrodes on the patient. These must be suitably marked for ready identification; as illustrated, one stripe, two stripes, three stripes, and four stripes identify, respectively, the terminal plug used for attaching the proper lead-wire to the right-arm, the left-arm, the left-leg, and the precordial (exploring) electrode.

H. Three 5,000-ohm, 1-watt resistors.

I. Three terminal binding posts (banana jacks) for attachment to the outside of the switch box.

J. One switch housing, for mounting and enclosing the composite switch. (A standard wooden filing box, as used for 3 by 5 inch index cards will serve satisfactorily for this purpose.)

K. Twelve marking tacks, ¼ inch in diameter, with celluloid-covered, flattened heads. These are used to identify the three terminal binding posts located on the outside of the switch box and the contact points about the switch bar-knob constituting the individual stations of the lead-selector, and can be properly marked for that purpose with India ink.

L. One 20-foot length of rubber-insulated, 26-strand wire, fitted with suitable contact points or clips, for use in grounding the switching device to an outside ground connection.

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*As manufactured by the Cambridge Instrument Company, Inc.

†For this purpose we have used Type U, 1 Pole 11 Position Steatite switch sections, and the Switchkit Index Assembly "K123," both manufactured by Centralab, Milwaukee, Wisconsin.

M. Four metal angle brackets, 1 by ½ by 1/16 inch, or other suitable means for fastening the switch box to the frame of the electrocardiograph or to the supporting table.

DETAILS OF CONSTRUCTION AND USE

The composite switch, mounted in a wooden box to protect the switch assembly and wiring, is shown in Fig. 1. This figure illustrates in perspective the clearly marked terminal plugs for attaching the lead-wires to the electrodes on the patient, the coupling connection used to convert the four lead-wires into the lead cable, the three terminal binding posts on the outside of the switch box (*G+*, *G–*, and *GND*), and the lead-selector consisting of the switch bar-knob and labelled stations. The switch bar-knob is located on the top face of the switch box and is encircled by markers located at the individual points of switch contact. These markers are clearly labelled *OFF*, *1*, *2*, *3*, *CF*, *CL*, *CR*, and *V*, respectively, in a clockwise manner and in this sequence, to form the individual stations of the lead-selector.

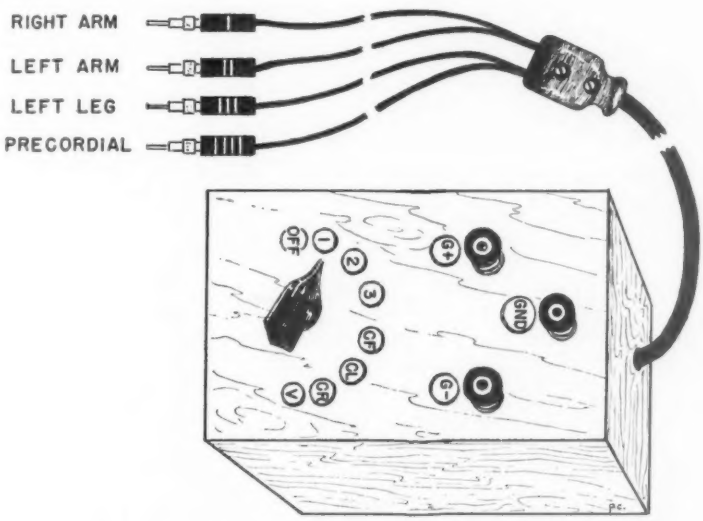

FIGURE I. THE COMPOSITE SWITCH

Fig. 2 is a diagrammatic representation of the assembled switch. The four switch sections are mounted in tandem on the same axis and are embodied in the switch assembly framework (latter not shown). The switch bar-knob is indicated mounted on the switch axis. The individual switch sections and the switch bar-knob are shown as widely separated in Fig. 2 in order that points of identification may be more clearly illustrated, but, in the actual construction, these units are mounted quite close together (not more than ½ inch apart), thereby reducing the overall size of the assembled switch. Also incorporated in this figure is a schematic representation of the wiring arrangements necessary to secure the proper circuit connections for Leads I, II, and III, and the CF, CL, CR, and V types of leads, respectively, with the use of this switch.

A complete wiring diagram for the switch herein described is shown in Fig. 3. In the text and in Figs. 2 and 3, in order to clarify the wiring description, the four individual switch sections are identified as Switches *A*, *B*, *C*, and *D*, respectively; the eight distributed points on each of the switch sections are identified, in a clockwise manner as seen from the top of the composite switch, as Points *0*, *1*, *2*, *3*, *4*, *5*, *6*, and *7*, respectively; and the common contact pole

on each switch section is identified as Point *X*. From the clearly marked terminal plugs, which serve for attaching the lead-wires to the electrodes on the patient, the four lead-wires pass by way of the four-wire microphone cable into the switch box, and are distributed as follows: The wire from the right-arm terminal plug goes to Points *1* and *2* on Switch *B*, thence to Point *6* on Switch

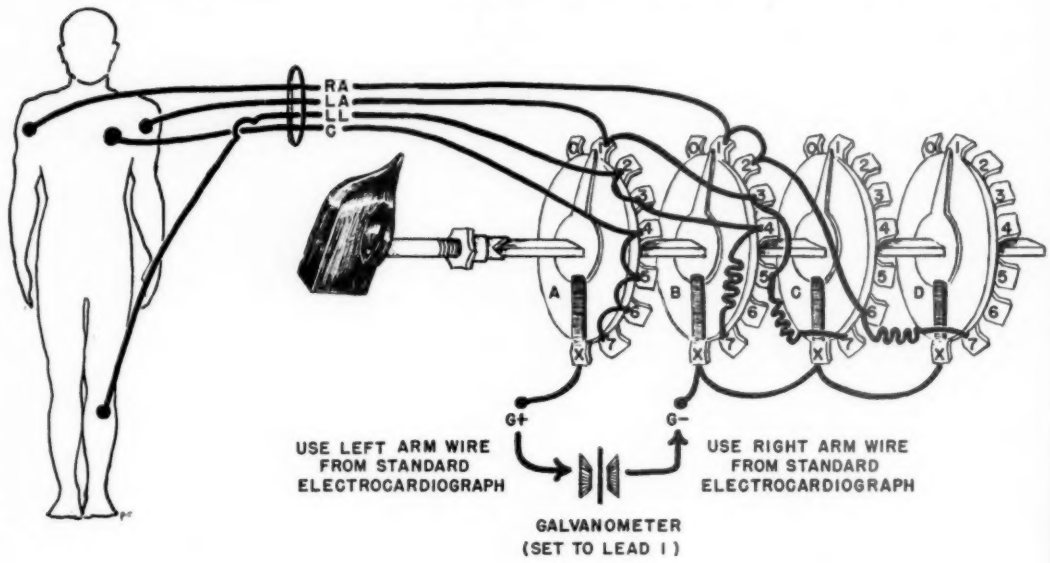

FIGURE 2. DIAGRAMMATIC DETAIL OF SWITCH CONSTRUCTION

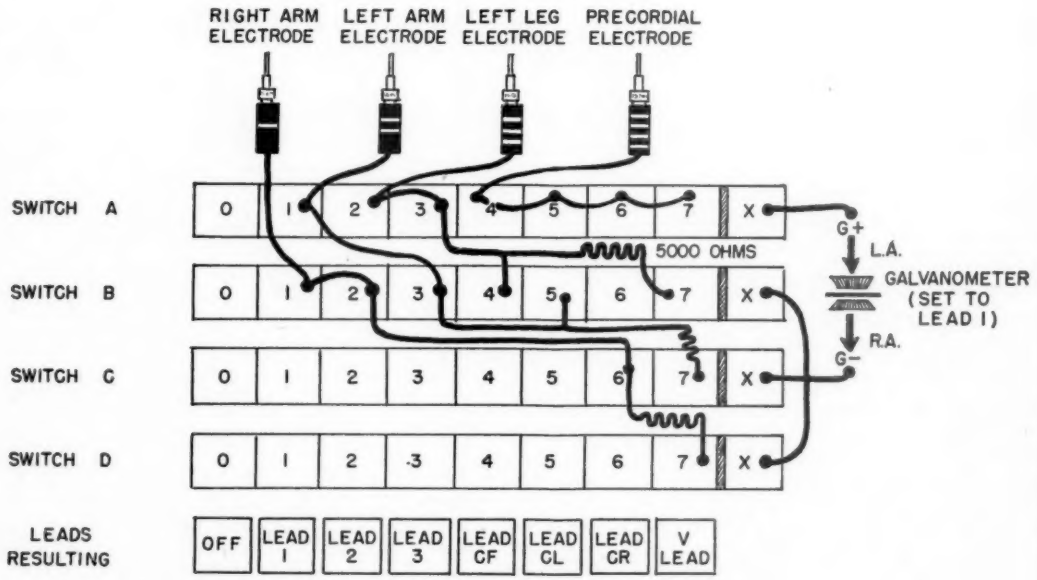

FIGURE 3. WIRING DIAGRAM

C, and finally through a resistor of 5,000 ohms to Point *7* on Switch *D;* the wire from the left-arm terminal plug goes to Point *1* on Switch *A*, thence to Points *3* and *5* on Switch *B*, and finally through a resistor of 5,000 ohms to Point *7* on

Switch *C;* the wire from the left-leg terminal plug goes to Points *2* and *3* on Switch *A,* thence to Point *4* on Switch *B,* and finally through a resistor of 5,000 ohms to Point *7* on Switch *B;* the wire from the precordial (or exploring) terminal plug goes to Points *4, 5, 6,* and *7* on Switch *A.* No wires are attached to the points labelled *O* on the switch sections, since these points constitute, in the composite switch, the *OFF* station of the lead-selector.

From the common contact pole (Point *X*) of Switch *A* a wire goes to the terminal binding post located on the outside of the switch box which is labelled *G+.* The common contact poles (Points *X*) of Switches *B, C,* and *D* are wired together, and the wire from these poles goes to the terminal binding post located on the outside of the switch box which is labelled *G–.* The switch assembly framework and the sheathing of the four-wire microphone cable are connected, by wires within the switch housing, to the terminal binding post, *GND,* located on the outside of the switch box. When the switching device is in actual use, a ground wire is extended from this binding post to a suitable outside ground connection. All permanent wiring connections within the switch housing are soldered to insure good contacts.

The switching device, as described, is so constructed and wired that proper polarity of the galvanometer, according to convention,[3, 4, 10] results for each lead indicated on the switch lead-selector when the device is correctly interposed in the circuit between the patient and a standard electrocardiograph. For this purpose, the lead-wires from the switching device are connected to the proper electrodes on the patient: the "left-arm" wire from the *electrocardiograph* is attached to the switch binding post, *G+;* the "right-arm" wire from the *electrocardiograph* is attached to the switch binding post, *G–;* and the lead-selector *of the electrocardiograph itself* is constantly set as ordinarily used for taking Lead I. Once these connections and adjustments have been made, each desired type of lead is recorded after selecting the correct station on the lead-selector of the switching device. The further operation of the electrocardiograph then proceeds in the ordinary manner. For recording the different types of multiple precordial leads, each desired type of lead is chosen on the switch lead-selector, and the exploring electrode is moved manually in succession to the correct precordial position.[3, 4] For recording the unipolar limb leads of Wilson and his co-workers,[6] the lead-selector of the switching device is set to Station *V,* and the exploring electrode is moved manually to some point on the right arm, left arm, and left leg, to yield Leads VR, VL, and VF, respectively.

The composite switch, constructed as described and enclosed in a protective housing or box, may be utilized as a completely portable device, or it may be fastened to the frame of the electrocardiograph or to the supporting table, by means of angle brackets, etc. With suitable modifications in construction, the switch proper may indeed be incorporated into the electrocardiograph itself. It is important that the arrangement provide the greatest measure of convenience in actual use, since that is the essential purpose which the switching device is designed to serve.

COMMENT

The switching device described in this paper was developed in order to record with convenience, for investigative purposes, individual electrocardiograms which embody Leads I, II, III, and IVF, the CF, CL, CR, and V types of leads from precordial positions 1 to 6, inclusive, and the V type of unipolar limb leads. With this device properly interposed in the circuit between the patient and any standard electrocardiograph, the correct wiring connections for

recording any or all types of this particular series of leads can be derived simply by rotating the lead-selector of the switch to the indicated stations, without the necessity for interchanging any of the lead-wires attached to the electrodes on the patient. In actual use, the device has proved highly satisfactory for the purposes for which it was developed. This switch, or modified versions thereof, has also been found to provide a considerable measure of convenience when employed in practical clinical electrocardiography. Combinations of Leads I, II, and III with V leads from the six recognized precordial positions are readily recorded with its use, and the V type of unipolar limb leads are easily added to this series when desired. Moreover, this device may be regarded as a prototype, and other similar switches may be devised from it, whereby any combination of different types of leads likely to be desired for clinical or investigative purposes can be recorded with facility. Thus, the switch can be modified so that a combination of the three limb leads, the V type of multiple precordial leads, and the Goldberger type of augmented unipolar limb leads,[7] may be conveniently obtained, if such a series of leads be desired.

In publishing directions for the construction and use of this switching device, we are motivated by a desire to render presently available standard electrocardiographic equipment, of any design, suitable for the convenient recording of electrocardiograms embodying multiple types of leads, in order to promote the more general utilization and study of such multiple lead electrocardiograms. It is hoped that, in this way, a solution to the present problem of the most useful combination of multiple types of leads for ordinary purposes in practical clinical electrocardiography will be facilitated. No claim is made that the design of this device embodies other than well-known electrical principles of switch construction.

SUMMARY

A switching device is described which can be constructed easily from readily obtainable materials and which, when properly interposed in the circuit between the patient and any standard electrocardiograph, permits the rapid and convenient recording of electrocardiograms embodying multiple types of leads, without the necessity for interchanging any of the lead-wires attached to the electrodes on the patient. Experience with this device has shown that it may be used with equal serviceability for investigative studies in electrocardiography or for ordinary clinical purposes.

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MICROSCOPIC LESIONS OF THE LEFT ATRIAL ENDOCARDIUM IN CHRONIC RHEUMATIC HEART DISEASE

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ENDOCARDITIS of the left atrium is a frequent and possibly constant lesion in acute rheumatic heart disease. The site of predilection is the posterior wall of the atrium, a short distance above the posterior mitral leaflet. Grossly, the endocardium is thickened, and its surface is opaque, rough, nodular, and the seat of numerous irregular ridges. Microscopically, there is usually diffuse change consisting of enlargement and hyperplasia of connective tissue cells, edema, degeneration of collagen, cellular exudate, and, in some instances, Aschoff nodules.

Most previous reports have been concerned mainly with the lesions of acute rheumatic endocarditis.[1-4] This study deals with the chronic or healed phase of the disease. The principal purpose was to determine what microscopic changes in these later lesions can be regarded as positive stigmas of rheumatic inflammation.

MATERIALS AND METHODS

Sections of the left atrium were obtained from one hundred nonrheumatic and one hundred rheumatic hearts. The rheumatic hearts were the seat of chronic or healed disease and showed no active gross lesions, i.e., verrucous endocarditis or fibrinous pericarditis. Seventy-five had mitral stenosis, and twenty-five had nondeforming mitral valvulitis. The latter consisted of thickening, opacity, and often vascularity of the valve leaflets without fusion or shortening; the chordae tendineae were also thickened. Several hearts with nondeforming mitral valvulitis showed slight aortic stenosis. Most of the hearts with mitral stenosis revealed deforming or nondeforming disease of other valves, especially the aortic and tricuspid valves. The nonrheumatic hearts were carefully selected, and those with equivocal gross rheumatic lesions rejected.

Only a single transverse section of left atrium, approximately 2.5 cm. in length, was studied. This was taken perpendicular to the endocardial surface and, according to the method of Gross, Antopol, and Sacks,[5] about 1 cm. above the attachment of the posterior mitral leaflet. There was close standardization of all sections with respect to size and location. The material was fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. In every case an extra section was stained with the combined Weigert and van Gieson methods for elastic and connective tissue.

In addition to the nonrheumatic and rheumatic groups, sections of left atrium were also made from twenty-five hearts with syphilitic aortic insufficiency and five hearts with atypical verrucous endocarditis.

The following items were studied: endocardium proper—thickness, subendothelial plaques, fibrosis, cellular hyperplasia of connective tissue, vascularity, cellular exudate,

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Aschoff nodules, thickness of smooth muscle, fibrinoid degeneration, mural thrombosis, and calcific deposit; subendocardium—thickness, vascularity, cellular exudate, and Aschoff nodules.

The thickness of the endocardium proper, the subendocardium, and the smooth muscle in the outer third of endocardium was determined by means of an ocular micrometer calibrated against a stage micrometer. Each reading was made at the thickest portion of each layer. With few exceptions the borders were well defined. The outer boundary* of the subendocardium was its junction with the auricular myocardium, but adipose tissue interposed between the subendocardium and the myocardium was not included. The measurement of smooth muscle was taken in a region where the cells were compact.

The degree of vascularity of the subendocardium was estimated by counting all the vessels in this layer.

THE NORMAL LEFT ATRIUM

The term endocardium is commonly used to denote the entire inner fibromuscular elastic layer of the left atrium, extending down to the auricular myocardium. However, for descriptive purposes this layer may be subdivided into two parts, i.e., the endocardium proper and the subendocardium. The former is conveniently subdivided further into three equal zones, an inner, middle, and outer third.[4] The inner third often shows superficial regions in which the elastica is sparse or absent. The outer third usually contains compact groups of smooth muscle cells arranged parallel to the elastic lamellae. Occasionally, small transverse or longitudinal bands of smooth muscle appear in the middle or inner thirds. The subendocardium lies immediately external to the endocardium proper and consists mainly of coarse bundles of collagen; its outermost part is often loose and fibrillar and merges with the stroma of the adjacent myocardium. Sometimes, in adults, it is separated from the muscle by small amounts of fat. The endocardium proper is avascular and shows no cellular exudate. The subendocardium usually contains a small number of capillaries and may reveal a few focal collections of lymphocytes.

DESCRIPTION OF RHEUMATIC LESIONS

Widening of the endocardium proper and the subendocardium results from inflammatory lesions such as cellular exudate, increased vascularity, and fibrosis. The increase in thickness of smooth muscle in the outer portion of endocardium proper is presumably due mainly to hypertrophy. The enlarged muscle cells contain vesicular nuclei which often show variation in polarity.

The subendothelial plaque, referred to by Gross[4] as endocardial reduplication, is a papillary mass, essentially fibrous, formed by proliferation of connective tissue in the innermost part of the endocardium. A distinction was made between the typical rheumatic plaque of papillary type and the slightly elevated or flat hyaline plaque of more or less uniform width. The latter was excluded since many normal hearts show this change owing to loss of superficial elastica.

As observed in this study, there are two main types of subendothelial plaque, the hyaline and the myxomatous or mucoid. The former usually consists of a compact, sparsely cellular mass of collagen or is composed of coarse, loosely arranged bundles of collagen. The myxomatous plaque has a delicate fibrillar matrix containing cells of oval, spindle, or stellate form.

In any variety of rheumatic plaque, elastic tissue may be absent or present in slight to considerable amount. The inner margin is sometimes covered by a coarse, elastic band. Although generally composed of only one layer of connective tissue, there are plaques of so-called multiple variety which consist of two or more distinct layers separated by an elastic membrane.

*The terms "outer" and "external" indicate a location toward the epicardium; "inner" and "internal" are toward the endocardial surface.

Fibrosis of the endocardium indicates proliferation of fibrous tissue or formation of scar resulting in distortion of architectural pattern and interruption of elastica. The change is focal, or patchy and diffuse, and may involve all portions of the endocardium. The fibrous lesions are often disposed obliquely or even perpendicular to the elastic lamina, are usually sparsely cellular, and sometimes accompanied by vascularity and cellular exudate.

Cellular hyperplasia of connective tissue refers to increased cellularity of endocardium and focal aggregates of mononuclear cells of histiocytic or fibroblastic type. The nuclei are vesicular or hyperchromatic, irregular in shape, often elongated, and may show palisading, while the cytoplasm is poorly defined. The polarity of the cells is variable, some being disposed obliquely, or even perpendicular, to the elastica. The intercellular collagenous matrix is sometimes the seat of swelling and degeneration.

Marked increase in vascularity of the subendocardium and vascular penetration of the endocardium proper are characteristic of rheumatic inflammation. Most of the vessels are capillaries or arterioles. A distinctive vascular lesion is observed occasionally, i.e., small arteries with thick musculoelastic wall.[4] These vessels are composed of concentric groups of longitudinal smooth muscle cells whose margins are often surrounded by elastic fibers. On cross section the artery has a honeycombed appearance.

Aschoff nodules consist of typical Aschoff cells, the Anitschkow myocytes, which have "owl-eyed," fibrocytoid, or pyknotic nuclei, distributed in an edematous matrix of swollen and coarsely granular collagen. The cytoplasm of the cells is frequently basophilic, and the cell outlines are irregular or ragged. Only nodules with typical morphology were accepted. Small groups of fibrocytes or histiocytes with normal cytoplasm and stroma were excluded.

In fibrinoid degeneration, the ground substance of connective tissue is converted to a fibrillar network or homogeneous structureless material which is poorly cellular, refractile, and intensely acidophilic.

CLINICAL DATA

All hearts were from adults. In the nonrheumatic group the ages ranged from 19 to 82 years; 52 patients were males and 48, females; 80 were white and 20, Negro. There was a variety of clinical diagnoses, such as carcinoma, pneumonia, diabetes, coronary thrombosis, and cor pulmonale. Twenty-five patients had hypertensive heart disease.

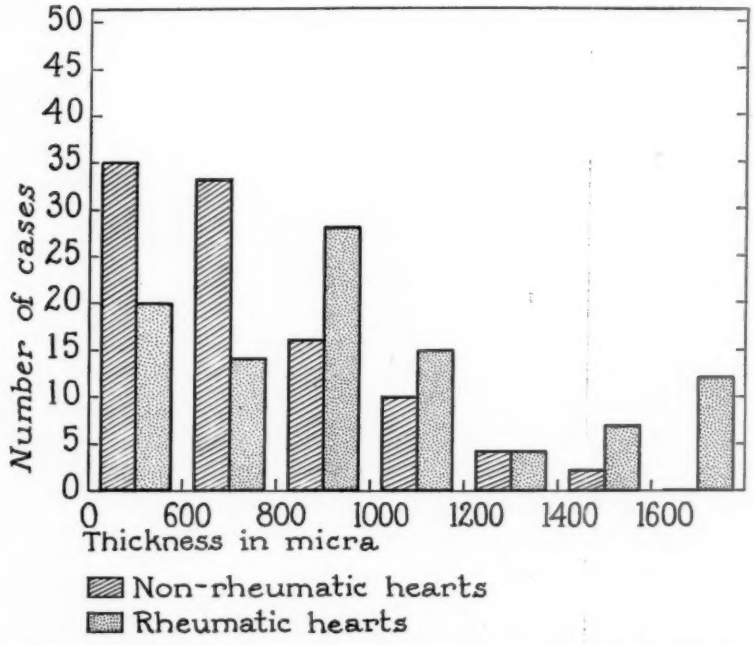
In the rheumatic group the ages varied from 22 to 78 years. There were 58 males and 42 females; 97 were white and 3, Negro. Most of the 75 patients with mitral stenosis had cardiac insufficiency of long duration with repeated attacks of decompensation and died of congestive failure. Most of the 25 nondeforming rheumatic lesions were incidental autopsy observations. None of the cases had a clinical diagnosis of active rheumatic disease.

RESULTS

A summary of the findings for nonrheumatic and rheumatic hearts is given in Tables I, II, III, IV, and V and Graphs I, II, and III. The following lesions were not observed in the nonrheumatic group: endocardium proper—subendothelial plaques with multiple layers, cellular hyperplasia of connective tissue, cellular exudate, Aschoff nodules, fibrinoid degeneration, mural thrombosis, and calcific deposit; subendocardium—small arteries with musculoelastic wall and Aschoff nodules.

TABLE I. LESIONS OF ENDOCARDIUM PROPER OF LEFT ATRIUM IN NONRHEUMATIC AND RHEUMATIC HEARTS

	100 NONRHEUMATIC HEARTS	100 RHEUMATIC HEARTS
Subendothelial plaque	6	23
Fibrosis	4	15
Cellular hyperplasia of connective tissue	0	18
Vascularity	2	25
Cellular exudate	0	21
Aschoff nodules	0	3
Fibrinoid degeneration	0	6
Mural thrombosis	0	5
Calcific deposit	0	1



Graph I.—Thickness of endocardium proper of left atrium in 100 nonrheumatic and 100 rheumatic hearts.

Endocardium Proper.—Thickness: In the nonrheumatic hearts the thickness of the endocardium proper varied from 330 to 1,440 microns (Graph I). The average thickness for one hundred cases was 753 microns. A value over 1,400 microns was obtained in only two hearts. The range in the rheumatic group was 330 to 3,180 microns with an average of 987. The thickness exceeded 1,400 microns in seven cases and was more than 1,600 microns in twelve cases.

Subendothelial Plaques: Plaques in subendothelial location, indistinguishable from those of rheumatic disease, were observed in six cases of the nonrheumatic group. Four were of hyaline type and two were mucoid. All plaques were of single layer variety, sparsely cellular, and contained elastic fibers, and two showed smooth muscle cells. None revealed vascularity or cellular exudate.

Subendothelial plaques were present in 23 of the 100 rheumatic hearts. In four cases there was a diffuse plaque involving almost the entire length of endocardium; in 18 cases the plaques were discrete and ranged from one to four in number per section. The plaques were of single layer type in 18 cases,

TABLE II. LESIONS OF SUBENDOCARDIUM OF LEFT ATRIUM IN NONRHEUMATIC AND RHEUMATIC HEARTS

	100 NONRHEUMATIC HEARTS	100 RHEUMATIC HEARTS
Vascularity (average number of vessels per section)	18	54
Musculoelastic arteries	0	6
Cellular exudate	3	22
Aschoff nodules	0	16

i.e.; dense hyaline, ten; loose hyaline, one; mucoid, four; and of both hyaline and mucoid variety, three. Plaques with two layers were present in four cases. In one instance there was a plaque with three distinct strata, a superficial mucoid superimposed upon two similar layers of dense collagen.

Elastic tissue was present in 12 and smooth muscle cells in 10 cases. Seven plaques of the single layer variety were covered superficially by a dense elastic membrane. Capillary vessels were observed in two cases, a slight cellular exudate of lymphocytes in five, and superimposed mural thrombosis in four cases.

Fibrosis: Fibrosis of the endocardium with distortion and interruption of elastica was observed in four nonrheumatic and in 15 rheumatic hearts. The lesions in each group were generally similar, except that vascularity and exudate were absent in hearts from the nonrheumatic group and present in eight of the 15 rheumatic cases.

Cellular Hyperplasia of Connective Tissue: Increased cellularity of endocardium with aggregates of swollen cells containing vesicular or hyperchromatic nuclei occurred in 18 rheumatic hearts. The collagenous matrix showed edema in 14 cases, swelling and granular degeneration in four, and cellular exudate in nine cases. Aschoff nodules were present in two cases.

Vascularity: The endocardium proper was vascularized in only two out of 100 nonrheumatic cases. In each instance a few capillaries were observed focally among smooth muscle cells in the outer third of endocardium. The middle and inner portions of endocardium were avascular in all cases.

Vascularity was present in 25 of the 100 rheumatic hearts. Most of the vessels were capillaries although two cases showed arterioles and small arteries with musculoelastic wall. The number of vessels in a single section varied from few to many and the distribution was focal or moderately diffuse. In 15 cases vascularity was confined to the outer third of the endocardium, in seven the middle third was also involved, while in three instances the capillaries penetrated into the inner third. In 15 cases the vascular change was associated with cellular exudate, usually slight and consisting mainly of lymphocytes with a few polymorphonuclear leucocytes. Focal perivascular fibrosis was present in eight cases.

Cellular Exudate: Twenty-one rheumatic cases showed this lesion which was usually focal and slight to moderate in degree. In three cases the change was diffuse and marked. The cells were mainly lymphocytes with occasional

TABLE III. AVERAGE THICKNESS, IN MICRONS, OF LAYERS OF ENDOCARDIUM OF LEFT ATRIUM IN NONRHEUMATIC AND RHEUMATIC HEARTS

	100 NONRHEUMATIC HEARTS	100 RHEUMATIC HEARTS
Endocardium proper	753	987
Smooth muscle	120	230
Subendocardium	235	373

TABLE IV. VASCULARITY OF SUBENDOCARDIUM OF LEFT ATRIUM IN NONRHEUMATIC AND RHEUMATIC HEARTS

NUMBER OF VESSELS PER SECTION	100 NONRHEUMATIC HEARTS	100 RHEUMATIC HEARTS
0 to 50	97	66
50 to 74	2	6
75 to 99	0	14
100 and over	1	14

polymorphonuclear leucocytes, plasma cells, and large mononuclear cells. The exudate was confined to the outer third of endocardium in eight cases, while the middle or inner thirds were also involved in 13 additional cases. Seventeen of the 21 cases showed capillary vascularity of the endocardium and the cellular infiltration generally occurred in the vicinity of the blood vessels.

Aschoff nodules: Typical nodules, of the so-called mosaic type, were present in the endocardium of three rheumatic hearts. They were situated in the inner third of endocardium in one case, in the outer third in one case, and in both middle and outer thirds in one case.

Thickness of Smooth Muscle: In the nonrheumatic group the average thickness of the smooth muscle layer in the outer third of endocardium was 235 microns as compared to 373 microns for the rheumatic cases (Table III). The range for the nonrheumatic group was 60 to 300 microns; for the rheumatic group, 60 to 540 microns. In ten rheumatic cases the value exceeded 300 microns (Graph II).

Fibrinoid Degeneration: This occurred in six rheumatic hearts and involved connective tissue in subendothelial location or in the inner third of endocardium proper. In four instances the lesion was situated within a subendothelial fibrous plaque at the base of a mural thrombus.

Mural Thrombosis: Mural thrombi of the left atrium were present in five rheumatic hearts. They were composed mainly of fibrin and erythrocytes with a relatively small number of platelets and leucocytes. In four cases the thrombi were superimposed on subendothelial plaques.

Calcific Deposit: This was present in one rheumatic heart which showed large, coarse, calcific masses within a subendothelial plaque of dense hyaline type.

Subendocardium.—Thickness: In the nonrheumatic group, the thickness of the subendocardium varied from 90 to 480 microns (Graph III). The average was 235 microns. Ninety cases measured less than 300 microns; there were only three over 400 and none over 500 microns. In the rheumatic group the range was 90 to 900 and the average was 373 microns. Sixteen cases measured more than 400, and 20 measured more than 500 microns.

Vascularity: A count was made of all blood vessels in the subendocardium. The average area of subendocardium per section was approximately 5.9 sq. mm. for the nonrheumatic hearts and 9.3 sq. mm. for the rheumatic hearts. The total vascularity is shown in Table IV. In the nonrheumatic group the number

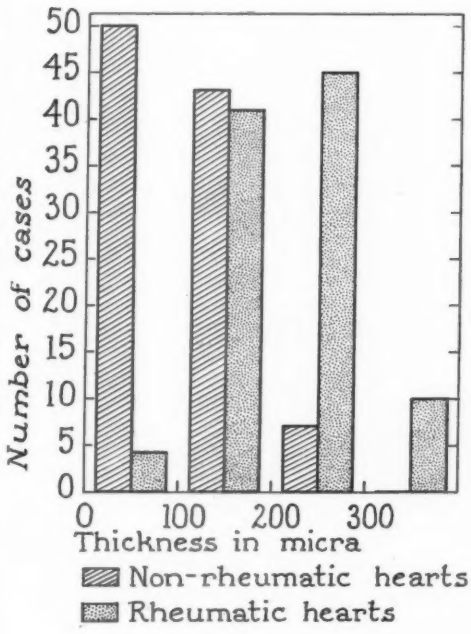
TABLE V. CELLULAR EXUDATE OF SUBENDOCARDIUM OF LEFT ATRIUM IN NONRHEUMATIC AND RHEUMATIC HEARTS

CELLULAR EXUDATE	100 NONRHEUMATIC HEARTS	100 RHEUMATIC HEARTS
None	75	38
Focal, slight	22	39
Focal, moderate or marked	3	4
Diffuse, moderate or marked	0	19

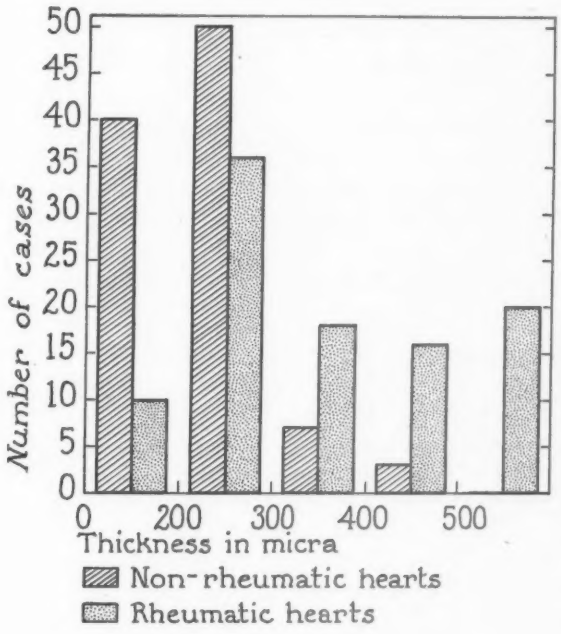
Number of cases

of blood vessels per section varied from 0 to 120 per section with an average of 18. There were less than 75 vessels in 99 cases, while one had 120. However, the last showed rheumatic valvular stigmas. No vessels with musculoelastic wall were observed. Among the rheumatic cases, the number of vessels ranged from 2 to 300 and the average was 54. More than 75 vessels were present in 14 cases and more than 100 in an additional 14. Six cases showed small arteries with thick musculoelastic wall.

The vascularity per unit area was as follows: 3.1 vessels per square millimeter of subendocardium in the nonrheumatic group and 5.8 vessels per square millimeter in the rheumatic group. The difference is statistically significant.



Graph II.



Graph III.

Graph II.—Thickness of smooth muscle layer of endocardium in 100 nonrheumatic and 100 rheumatic hearts.

Graph III.—Thickness of subendocardium of left atrium in 100 nonrheumatic and 100 rheumatic hearts.

Cellular Exudate: Of the nonrheumatic group 75 cases contained no cellular exudate in the subendocardium. Twenty-five had focal infiltration, mainly of lymphocytes and usually in the vicinity of blood vessels. This was slight and inconspicuous in 22 cases and prominent in three cases. There was no instance of diffuse exudate. In contrast, 19 rheumatic cases showed widespread exudate of moderate to marked degree (Table V).

Aschoff Nodules: Sixteen rheumatic hearts revealed subendocardial Aschoff nodules. For the size of field given previously, the number of nodules varied from 1 to 8 per section with an average of 3.3. They were usually of mosaic or reticular mosaic type with a few coronal or polaroid forms.[6] Nuclei of fibrocytoid, hyperchromatic, and "owl-eyed" type were usually present in each nodule, with the first the most frequent. The cytoplasm of the cells was frequently basophilic, and the cell margins were ragged and irregular. The connective tissue matrix showed edema and fragmentation but fibrinoid degeneration was not observed. Slight cellular infiltration was present in one or more nodules in seven cases.

Rheumatic stigmas of the left atrium were absent in the hearts of 25 persons with syphilitic disease, and also in the hearts of five persons with atypical verrucous endocarditis except for one case with a large subendothelial plaque.

DISCUSSION OF RESULTS

Among the nonrheumatic group were 12 hearts in which the left atrium showed one or more lesions of rheumatic type. There was a total of 18 such lesions (Tables I, II, IV, and V and Graphs I and III). To determine whether these were uncommon normal variations in structure or actually due to rheumatic disease, the 12 hearts were examined for rheumatic stigmas elsewhere than in left atrium, especially the valves. In the latter the presence of vascularity, cellular exudate, and fibrosis, especially fibroelastic reduplications of auricularis or ventricularis layers, was considered indicative of rheumatic disease.

Acceptable valvular stigmas were present in four of the 12 hearts. This leaves eight hearts not established as rheumatic with the following lesions: subendothelial plaque, four; endocardial fibrosis, three; vascularity of endocardium proper, one; thick endocardium proper, one; thick subendocardium, one; cellular exudate of subendocardium, one. Possibly these are instances of rheumatic disease with stigmas confined to the left atrium.

Some rheumatic lesions resemble and may be indistinguishable from alterations in structure of the normal atrium. This refers especially to subendothelial plaques, endocardial fibrosis, and increase in thickness of the smooth muscle. Gross[4] pointed out that, from the third decade on, thickening of smooth muscle and progressive loss of elastic tissue are commonly observed in the atrial endocardium. Loss of elastica in subendothelial location or inner third of endocardium often gives the appearance of subendothelial plaque or scar. Other rheumatic changes, such as widening of the layers of endocardium and increased vascularity and cellular exudate of subendocardium, may also be confused with normal variations. While lesions, especially if multiple, may suggest rheumatic disease, they cannot be regarded per se as characteristic unless well developed and beyond the normal range.

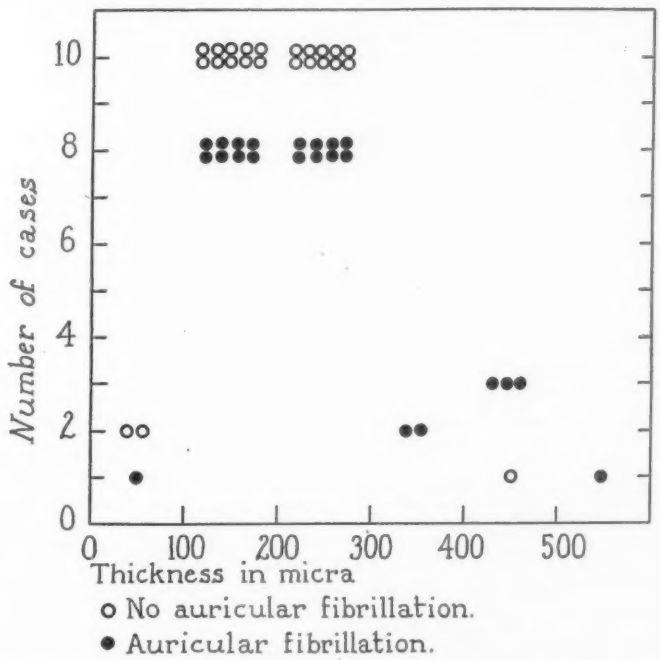
Several microscopic lesions which occur very rarely, if at all, in normal hearts or in other forms of heart disease, are practically pathognomonic of rheumatic endocarditis. The most frequent in the endocardium proper are vascular penetration, cellular exudate, and cellular hyperplasia of connective tissue; in the subendocardium the most frequent are extensive vascularity, including the presence of vessels with musculoelastic wall, and Aschoff nodules. Other changes, such as subendothelial plaques with multiple layers, fibrinoid degeneration, and calcific deposit, while conclusive, are comparatively infrequent. Gross[4] emphasized endocardial reduplications, vascularity of endocardium, and increase of endocardial smooth muscle as highly suggestive of rheumatic endocarditis in hearts with inactive disease. The atrial lesions of lupus erythematosis differ from those of rheumatic fever.[7]

Sixty rheumatic hearts showed one or more conclusive stigmas in the left atrium, while 40 were negative or equivocal. Most of the equivocal changes were probably rheumatic but not distinctive. As in the valves, rheumatic atrial disease, especially if slight, may heal without leaving diagnostic lesions.

The stigmas of rheumatic disease are usually multiple. Of 60 positive hearts, 34 had three or more stigmas, eight had two, and 18 had only one. In the last group the principal lesions were Aschoff nodules, vascularity of

endocardium, extensive vascularity of subendocardium, and subendothelial plaques.

In well-developed rheumatic disease there is often conspicuous thickening of the endocardial smooth muscle. Hutcheson[8] suggested that this might lead to auricular fibrillation if the smooth muscle became preponderant over the striated muscle of the atrial myocardium. Our figures in this connection are of limited value since there were electrocardiograms in only 46 cases. In 23 patients with auricular fibrillation the thickness of smooth muscle varied from 90 to 510 microns with an average of 256. For 23 patients without auricular fibrillation the range was 60 to 480 microns and the average 206. The distribution curves do not show a significant difference between the two groups (Graph IV). This was also true with respect to the thickness of atrial myocardium. In the hearts with auricular fibrillation there was no constant relation between thickness of myocardium and endocardial smooth muscle.



Graph IV.—Relation of auricular fibrillation to thickness of smooth muscle of endocardium.

Formation of new blood vessels is often a prominent feature of rheumatic atrial endocarditis. This occurs in the acute phase of the disease and the vessels remain as a stigma when activity ceases. The increase in vascularity varies from slight to marked and involves principally the subendocardium, although sometimes there is vascular penetration of the endocardium proper. While most of the new vessels are capillaries, a small number of cases show arterioles, or small arteries, with thick musculoelastic wall. The latter which are found more frequently in the valves, especially mitral, than elsewhere in the heart are especially characteristic of rheumatic disease.

Such lesions as cellular hyperplasia of connective tissue, sometimes associated with degeneration of collagen, and Aschoff nodules, indicate activity of the rheumatic inflammation. The degree and extent of cellular proliferation observed in this study were slight compared to the well-developed lesion gen-

erally present in acute rheumatic endocarditis. In the latter the change is diffuse and the hyperplasia of connective tissue cells is accompanied by palisading, swelling and fibrinoid degeneration of collagen, edema, and infiltration of polymorphonuclear leucocytes and lymphocytes.

Aschoff nodules are pathognomonic of rheumatic heart disease. This refers to the typical lesions and not to the so-called Aschoff-like or sub-Aschoff nodules[9] which lack precise identity. In this study the subendocardial layer of left atrium contained nodules more frequently than endocardium proper or atrial myocardium and less frequently than the myocardium of left ventricle, i.e., sixteen as compared to twenty-three cases. However, there were several hearts in which the lesion was apparently confined to the subendocardial portion of the atrium.

Fibrinoid degeneration is described as the principal change in the ground substance of connective tissue in acute rheumatic inflammation.[10] As such, the lesion was not present in this series of chronic rheumatic hearts, although a small number of cases showed fibrinoid, mainly within subendothelial fibrous plaques. The exact nature of the lesion, whether a primary degeneration of connective tissue[11-13] or due to deposition of fibrin,[14] or a combination of these,[15] is not clearly established.

Of interest is the possible relation of the rheumatic subendothelial plaque to atrial myxoma. There is a question as to whether the latter is a true neoplasm or a new growth of inflammatory type, originating in connective tissue. Dexter and Work[16] point out that a rheumatic lesion of the posterior or septal wall of the left atrium may leave a residuum on which granulation tissue develops, ultimately producing the tumor mass. In the case of myxoma which they reported, the heart showed signs of extinct rheumatic disease.

COMMENT

Stigmas of chronic rheumatic disease occur more frequently and with greater variety in the endocardial layer of the left atrium than in the myocardium or pericardium. In the latter, the only positive stigma is the Aschoff nodule; vascular lesions, fibrosis, and cellular exudate are generally not sufficient for diagnosis. Although 60 of the 100 rheumatic hearts in this study had definite stigmas in the endocardium, only five revealed positive lesions, i.e., Aschoff nodules, in the atrial myocardium.

The correlation between gross and microscopic findings is shown by the following figures: of 42 hearts with gross rheumatic disease of the left atrium, 40 showed conclusive microscopic stigmas and 2 were equivocal. Of 58 hearts with doubtful gross lesion or grossly normal, 20 were positive microscopically. Thus, microscopic study may indicate rheumatic endocarditis even though the gross change is not diagnostic.

The distribution of microscopic lesions of the valves, left ventricle, and left atrium of the one hundred rheumatic hearts is shown in Table VI. The mitral valve is uniformly positive because only hearts with gross mitral lesions were selected. Stigmas of the left atrium were approximately as frequent as those of aortic and tricuspid valves and were more frequent than in pulmonary valve and left ventricle.

Hearts with well-developed, left atrial endocarditis are usually the seat of more or less widespread rheumatic involvement. All sixty hearts with atrial stigmas showed lesions in other sites, i.e.: mitral valve, 60 cases; aortic valve, 57; tricuspid valve, 42; pulmonary valve, 32; and left ventricle, 23. Three

TABLE VI. DISTRIBUTION OF MICROSCOPIC STIGMAS IN 100 CASES OF CHRONIC RHEUMATIC HEART DISEASE

	NUMBER OF CASES WITH POSITIVE STIGMAS
Mitral valve	100
Aortic valve	69
Tricuspid valve	60
Left atrium	60
Pulmonary valve	40
Left ventricle (Aschoff nodules)	26

or more of these sites were positive in 48 cases, two sites in nine cases, and only one site, the mitral valve, in four cases. Moreover, the incidence of positive stigmas in the atrium is related to the severity of the valvular disease, especially mitral. In this study, the atrium was involved in 54 of 75 hearts with mitral stenosis (72 per cent) and in only six of 25 hearts with nondeforming mitral valvulitis (24 per cent).

This limits the practical value of the atrial endocardium as a site for diagnostic stigmas of chronic rheumatic disease. When the atrium is positive there are generally clear cut valvular lesions, while in cases with slight or doubtful disease of valves the atrium is often negative. However, typical lesions of the atrium may occur in hearts with nondeforming valvulitis. Occasionally, atrial stigmas aid in establishing rheumatic disease in hearts with equivocal valvular change.

Although hearts with gross evidence of active rheumatic disease were excluded, a fairly large number—about 20 per cent—showed one or more active lesions microscopically, i.e., Aschoff nodules, cellular hyperplasia of connective tissue, and swelling and degeneration of collagen. In a few of these there was focal verrucous endocarditis of valves not recognized in gross. A clear distinction between active and acute disease is often difficult. Such lesions may indicate a recently superimposed acute rheumatic attack, or persistent activity of a previous acute attack, or possibly reactivation, especially in the stage of cardiac failure.

SUMMARY AND CONCLUSIONS

In 100 hearts, the seat of chronic rheumatic disease, there was gross involvement of the left atrial endocardium in 42 cases and microscopic involvement in 60 cases.

Certain microscopic lesions of the endocardium of the left atrium, which occur rarely, if at all, in normal hearts or in other types of cardiac disease, form practically pathognomonic stigmas of rheumatic endocarditis. In the endocardium proper these include vascular penetration, cellular exudate, and cellular hyperplasia of connective tissue; in the subendocardium they include excessive vascularity and cellular exudate, the presence of small arteries with musculoelastic wall, and Aschoff nodules.

Other lesions, such as subendothelial plaque, endocardial fibrosis, and increase in thickness of smooth muscle, may be highly suggestive of rheumatic disease but require differentiation from corresponding alterations in structure of the normal endocardium.

Rheumatic endocarditis of the left atrium usually occurs in hearts with deformity of the mitral valve and with more or less widely distributed microscopic rheumatic stigmas, especially of the valves. In occasional instances, however, atrial stigmas aid in establishing rheumatic fever as the cause of equivocal valvular disease.

Comparison of small groups of cases with and without auricular fibrillation showed no significant difference in the thickness of endocardial smooth muscle.

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Clinical Reports

VENTRICULAR FIBRILLATION AS A COMPLICATION OF HYPERTHYROIDISM

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CHARLESTON, S. C.

ALL OF the authors who have described the disturbances of the heart which occur in hyperthyroidism have emphasized the fact that auricular fibrillation is the arrhythmia most commonly encountered. Transitory auricular flutter and A-V block have been noted as exceptional occurrences.[1, 2] Although the ability of thyroxin to increase the irritability of the myocardium is well known, I have been unable to find any mention in the American literature of clinical observations of arrhythmias arising from ventricular disturbances in this disease.

In Europe, Bickel[3] described two cases of sudden death in hyperthyroidism from cardiac arrest. Both patients were autopsied, but in neither was electrocardiographic proof obtained. Both deaths occurred after digitalization, and ventricular fibrillation was suggested as the cause. In Argentina, Sabathie[4] described a case of "ventricular *pre*fibrillation" in hyperthyroidism. One electrocardiogram showed auricular fibrillation, left bundle branch block, and runs of ventricular tachycardia. Another showed numerous extrasystoles from multiple ventricular foci. Five days after subtotal thyroidectomy there were found normal sinus rhythm, first degree A-V block, left bundle branch block, and occasional ventricular extrasystoles. Similar findings were obtained fourteen months later.

Bickel and Frommel[5] obtained sinus tachycardia, auricular and ventricular extrasystoles, auricular fibrillation, ventricular tachycardia, and ventricular fibrillation, all proved electrocardiographically, after massive injections of thyroid extract in rabbits. However, these results were obtained with crude extracts of thyroid glands, and all occurred within a matter of minutes after injection. Since it is well known that a latent period of twenty-four to forty-eight hours must elapse between the administration of thyroxin and the occurrence of any demonstrable biologic effect, it seems doubtful that the production of ventricular fibrillation in these experiments can be ascribed to the action of thyroxin.

Fig. 1 is an electrocardiogram obtained from a patient with recurrent hyperthyroidism. It is believed that this is the first proved instance of ventricular fibrillation in hyperthyroidism to be reported.

REPORT OF CASE

Hospital No. 11458. Mrs. L. J., a 37-year-old housewife, separated from her husband, entered the Roper Hospital Aug. 17, 1942, complaining of nervousness and asthma. When she

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first became very nervous, she was 17 years of age and was employed as a telephone operator. A diagnosis of hyperthyroidism was made, and a subtotal thyroidectomy was done. After this her nervousness disappeared for some years. But after many worries and an unhappy married life, her nervousness reappeared two years before admission. At this time she suffered a severe attack of "double pneumonia." Following this, in addition to nervousness, she began having occasional attacks of difficult breathing and coughing which occurred mostly at night. These attacks had become much more frequent and severe. At 4 A.M. the morning of admission, an especially severe attack of her "asthma" began. It was accompanied by protracted nausea and vomiting. She was referred to the Roper Hospital by her private physician.

Past history disclosed asthma in childhood which had never recurred, removal of tonsils and adenoids in childhood, appendectomy at 10 years, and salpingo-oophorectomy at 23 years. She also had had myopia since childhood requiring glasses for correction, frequent colds in the preceding two years, and menorrhagia for sixteen years. The family history was noncontributory.

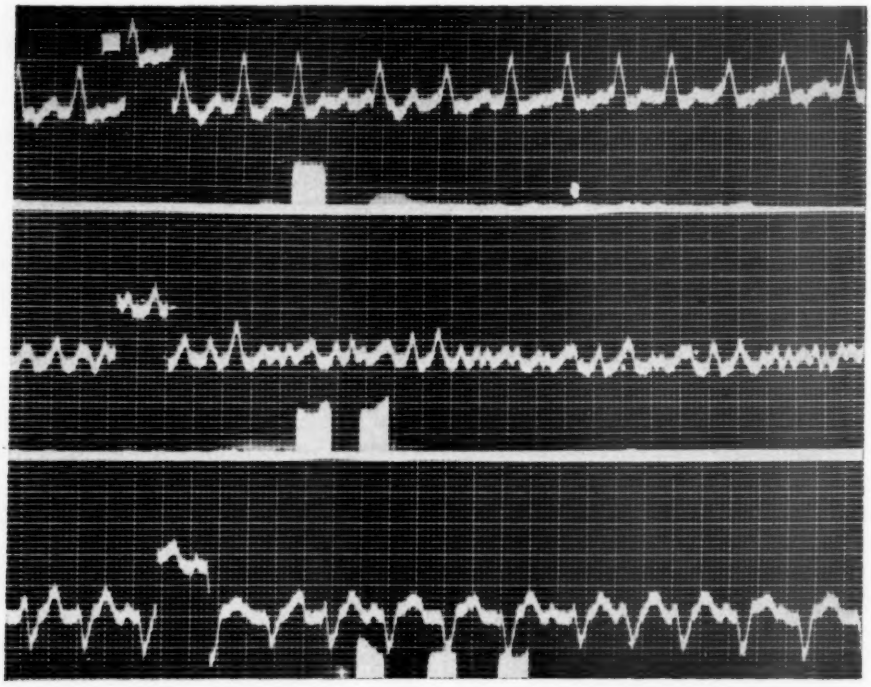

Fig. 1.

Physical examination showed a well-developed but thin, pale, nervous, and apprehensive woman of about 40 years. Her skin was fine in texture, moist, and warm. Her eyes were normal aside from myopia; there was no exophthalmos. Her tongue was rather red in color and clean, the edges were atrophic, and there was a fine tremor on protrusion. Her neck showed a scar of previous thyroidectomy. The thyroid gland was moderately enlarged, more so in the right lobe and isthmus, and was quite firm and slightly nodular. Scattered moist râles and a few musical rhonchi were heard throughout both lung fields. The heart was slightly enlarged, but there were no murmurs. The heart rate was 130 per minute, regular, but a pulse deficit of 20 was observed. The peripheral arteries were normal; the blood pressure was 150/75. The abdomen was normal except for scars of two previous operations. The extremities showed a fine tremor of the extended fingers. There was no edema. The reflexes were hyperactive.

Laboratory studies were as follows:

Urine:

Aug. 17, 1942: specific gravity, 1.020; albumin, 1 plus; sugar, 1 plus; acetone, 4 plus; and sediment, negative.

Aug. 19, 1942: specific gravity, 1.010; albumin, 1 plus; sugar, 1 plus; acetone, 0; and sediment, negative.

Blood:

Aug. 17, 1942: red blood cell count, 3,300,000; hemoglobin, 13 Gm.; white blood cell count, 6,700; polymorphs, 65 per cent; lymphocytes, 30 per cent; and monocytes, 5 per cent.

Aug. 18, 1942: Wassermann and Kline reactions negative. Cholesterol, 178 mg. per cent.

Aug. 27, 1942: blood sugar, 84 mg. per cent.

Significant excerpts from the progress notes were as follows: Aug. 19, 1942: Before daybreak on the morning of admission, the patient experienced a sudden attack of paroxysmal rapid heart action accompanied by an obstructive type of dyspnea and a sensation of choking in the throat. Examination showed that the lungs were clear without asthmatic wheezes. There was rapid tumultuous heart action, grossly irregular, and the rate was 150 to 160. The pulse rate, at the wrist, was 120; the pulse deficit was 30 to 40. The electrocardiogram (Fig. 1) showed auricular flutter, A-V dissociation, and intraventricular block. Lead II appears to consist entirely of a period of ventricular fibrillation. The patient stated that her "asthma" was a sensation of something pressing about her lower neck. She seemed nervous and despondent. Lugol's solution, 15 minims three times daily, was prescribed.

Aug. 20, 1942: The pulse and heart rate was 116 per minute. There was no deficit or irregularity. The patient slept well the preceding night and her nerves were calmer.

Aug. 21, 1942: The heart rate was regular; there was a systolic gallop at the apex; the rate was 100 to 120; and there was no pulse deficit. The electrocardiogram showed sinus rhythm, intraventricular block, and varying A-V block.

Aug. 25, 1942: The heart rate was regular, 100 per minute. The basal metabolism was +39 per cent.

Aug. 27, 1942: The heart rate was regular, 108 per minute. The basal metabolism was +27 per cent.

Sept. 4, 1942: Practically the whole right lobe of the thyroid was extirpated.

Oct. 24, 1942: The basal metabolism was +24 per cent.

Oct. 27, 1942: The left lobe of the thyroid was removed except for a narrow strip of normal appearing tissue behind the trachea.

Oct. 30, 1942: The patient felt very well. Her pulse was 88 per minute, her blood pressure, 140/90.

Oct. 31, 1942: The patient was discharged from the hospital.

DISCUSSION

Aside from the period of ventricular fibrillation in the tracing reproduced here, the underlying rhythm was at first assumed to be ventricular tachycardia. But a second tracing, after normal sinus rhythm was restored, showed the ventricular complexes to be of the same character as those in the first tracing, so that auricular flutter, A-V dissociation, and A-V nodal tachycardia with intraventricular conduction delay seemed to be the better interpretation. Unfortunately the technical quality of the second tracing is too poor to permit photographing for reproduction.

The present author is of the opinion that paroxysmal ventricular fibrillation may not be as unusual an event in the course of hyperthyroidism as this first case report might indicate. Since in man the diagnosis is next to impossible to make unless the patient happens to be connected to an electrocardiograph at the time the paroxysm occurs, it is possible that many instances of this arrhythmia have in the past occurred and been passed off clinically as auricular fibrillation. Such indeed was the assumption in the case presented, until the electrocardiogram unexpectedly brought to light the true nature of the arrhythmia.

Bickel[3] noted that his cases of cardiac arrest occurred after full digitalization, and felt that digitalis was contraindicated in thyrocardiac disturbances because of its effect in further increasing myocardial excitability. In this connection it should be noted that this patient received no digitalis at any time, and that the arrhythmia quickly disappeared after the administration of Lugol's solution was begun.

Sudden death in hyperthyroidism is certainly not unknown, and this was especially true in the days before Plummer's epochal discovery of the quieting effect of iodine. Moreover, a definite impression seems to have grown up among many clinicians working in large thyroid clinics that digitalis is not only ineffective, but possibly even harmful in thyrocardiac disturbances. It does not seem unreasonable to link these observations in the following conclusions.

CONCLUSIONS

1. The increased myocardial excitability in hyperthyroidism may occasionally lead to paroxysms of ventricular fibrillation.

2. Iodine is a safer and more effective drug than digitalis in controlling the arrhythmias of hyperthyroidism.

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ACUTE ISOLATED MYOCARDITIS

Report of a Case Due to Micro-Aerophylic Streptococcus Hemolyticus

John R. Schenken, M.D., and Winston C. Heibner, M.D.
New Orleans, La.

ACUTE isolated myocarditis or Fiedler's myocarditis is a disease which is usually characterized clinically by the sudden onset of dyspnea, cyanosis, and precordial pain, and which usually terminates fatally within a few days. In some cases, however, the onset is gradual, and, in others, the illness is protracted over a period of several months.

From a pathologic standpoint it may be defined as a "disease in which inflammation of the myocardium is the only important active acute lesion in the body"[1] and in which there is an "absence of any major pathologic condition involving either the endocardium or pericardium."[2] Anatomically it is not a specific form of myocarditis but is classified as a separate entity largely because the etiology is unknown.

The pathologic lesions in many cases of myocarditis where the etiology is known are indistinguishable from those in acute isolated myocarditis.

In a recent extensive review of the literature on isolated myocarditis, Saphir[2] stated that ". . . two distinct types of myocarditis have been described. One is characterized by the presence of granulomatous lesions and the other by

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a more diffuse type of inflammation. . . ." It is possible that these two types may represent disease processes of different etiology, but since their separation on anatomic grounds alone is not justified they are still considered as variants of the same disease.

The vast majority of the cases which are reported in the literature has been diagnosed on the basis of the microscopic examination. The search for a causative infectious agent has been inadequate because the disease is difficult to recognize clinically and macroscopically at necropsy.

We have recently observed a case of the diffuse type of isolated myocarditis which we recognized grossly because of the rather striking macroscopic appearance. We isolated a micro-aerophylic *Streptococcus hemolyticus* in pure culture from the heart muscle.

Our review of the literature has failed to reveal any other instance where a pyogenic organism was proved to be responsible for isolated myocarditis.

REPORT OF CASE

A 16-year-old, white, American male of Jewish descent was admitted to the hospital Dec. 24, 1942, at 7:20 P.M. and died Dec. 25, 1942, at 10:20 A.M. His chief complaint was pain in the chest. On the afternoon of admission while playing basketball, the patient suddenly experienced great difficulty in breathing, saw spots before his eyes, became dizzy, and fell to the floor. He had never had any serious illnesses before, had been a regular member of the basketball team, and had been able to perform strenuous tasks without difficulty.

Physical examination revealed that the skin was cold and clammy. His blood pressure was 70/40, pulse rate 110 per minute, and temperature 98° F. He was given immediately 1,000 c.c. of 10 per cent glucose intravenously, and, following this infusion, his blood pressure rose to 90/70. Examination of the heart at this time revealed that the pulmonic second sound was louder than the aortic second sound. The mitral first sound was prolonged, but no murmurs were heard. Examination of the lungs revealed crepitant râles and a wheezing expiration. Eight hours after admission the patient was still in shock. The pulse was rapid and thready, the neck veins were distended, and the nail beds as well as the skin over the face and neck were cyanotic. He intermittently beat his chest with his hands and cried, "The pain is killing me." Coarse râles were heard over both lung bases. Just before death, which occurred about eighteen hours after the onset of illness, large amounts of pink, frothy material poured forth from the nose and mouth.

Laboratory Examination.—An x-ray film of the chest was made shortly after admission, and the following report was given: "There is a slight increase in the transverse diameter of the heart. No shift of the mediastinal structures can be detected. The vascular markings are accentuated throughout both lungs and there is a mottled clouding of the parenchyma, the impression being that of pulmonary congestion and edema. A flat plate of the abdomen reveals marked gastric dilatation." No other laboratory examinations were made.

Post-Mortem Examination.—The body was that of a well-developed and well-nourished white male, measuring 165 cm. in length and weighing 54.5 kilograms. A pinkish-white froth filled the nasal and oral cavities. The superficial veins of the neck were markedly distended. The skin of the face and neck, the mucous membranes, and the nail beds were deeply cyanotic. There was no edema of the extremities or the back.

The peritoneal cavity contained about 40 c.c., each thoracic cavity contained 500 c.c., and the pericardial sac contained about 50 c.c. of a clear, straw-colored fluid. No exudate was present upon the serous membranes.

The right lung weighed 620 grams and the left, 460 grams. Each lung showed similar findings. Pinkish-white froth filled the large bronchi, and clear fluid poured forth from the cut surface. There was no evidence of consolidation. The liver weighed 1,212 grams. The capsule was smooth, the margins sharp, and the cut surface revealed normal color and markings. The gall bladder and bile ducts were normal. The spleen weighed 150 grams, and its capsule was smooth. The cut surface was irregular and deep purple in color; the pulp was softer than normal, but the markings were preserved. The right kidney weighed 112 grams, and the left, 125 grams. A moderate degree of congestion was the only finding of note. The pancreas, suprarenal glands, urinary bladder, gastrointestinal tract, and testes appeared normal.

The heart weighed 225 grams. The chambers of the heart appeared to be moderately dilated. The endocardium was smooth and glistening, and the valves appeared normal. The myocardium was somewhat flabby. The cut surface of the left ventricle and the left ventricular side of the interventricular septum showed a zone of brownish-red muscle directly beneath the endocardium (Fig. 1). This zone, which extended from apex to base and measured 0.5 to 0.6 cm. in thickness, did not reach the endocardium at any point but remained about 0.1 to 0.2 cm. beneath it. The myocardium of the right ventricle did not show these changes. The coronary vessels were carefully inspected by serial cross sections and were widely patent throughout.

Microscopic Examination.—The lungs showed large quantities of fluid mixed with varying numbers of red blood cells in the alveolar sacs. No exudate was present. No macrophages were noted. The alveolar capillaries were dilated but there was no evidence of interstitial inflammation. The only finding in the liver was a separation of the sinusoidal walls from the liver cords. There was no evidence of chronic passive congestion. The spleen showed a moderate congestion of the pulp with an increased number of polymorphonuclear leucocytes. One Malpighian corpuscle in each section showed a central area of reticulum cell hyperplasia and necrosis. The remaining organs appeared normal.

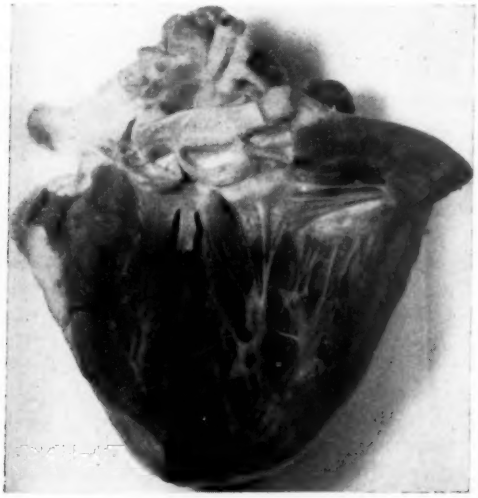

Fig. 1.—Photograph of the left ventricle and interventricular septum of the heart. The chamber is dilated. Note the dark mottled zone beneath the endocardium.

Although the lesions in the heart were present predominantly in the mottled zone beneath the endocardium (Fig. 2), changes in the myocardium were present throughout the entire thickness of the musculature from the pericardium to the endocardium. Neither of these surfaces was inflamed. The location and the distribution of the lesions were quite irregular.

The areas showing the alteration in the muscle fibers were distributed in a patchy fashion. Some of these patches were surrounded by normal appearing muscle fibers. The changes in the muscle fibers were, for the most part, degenerative changes with the preservation of their general contour. In some areas there were irregular thickenings of the muscle fibers due to localized points of hyalinization, whereas in other areas rather long lengths of muscle fibers showed a loss of cross and longitudinal striations as the result of a rather uniform hyalinization. In both areas, however, the fibers stained more deeply than normal with eosin. In some areas the fibers showed an increase in the granularity, often revealing irregular, coarse granules and irregular, thick intercalated discs, as well as pale staining granular areas alternating with deep red staining hyalinized areas.

Inflammatory cell infiltration was associated with these degenerative changes (Fig. 3). In most areas this infiltration was rather mild, consisting largely of rows of polymorphonuclear leucocytes and a few macrophages between the muscle fibers. In other areas, however, very tiny foci of inflammatory cells were present at a point where there was obviously a defect in the continuity of the muscle fiber. None of these areas was large enough to be classified as an abscess. The densest points of accumulation of inflammatory cells were in

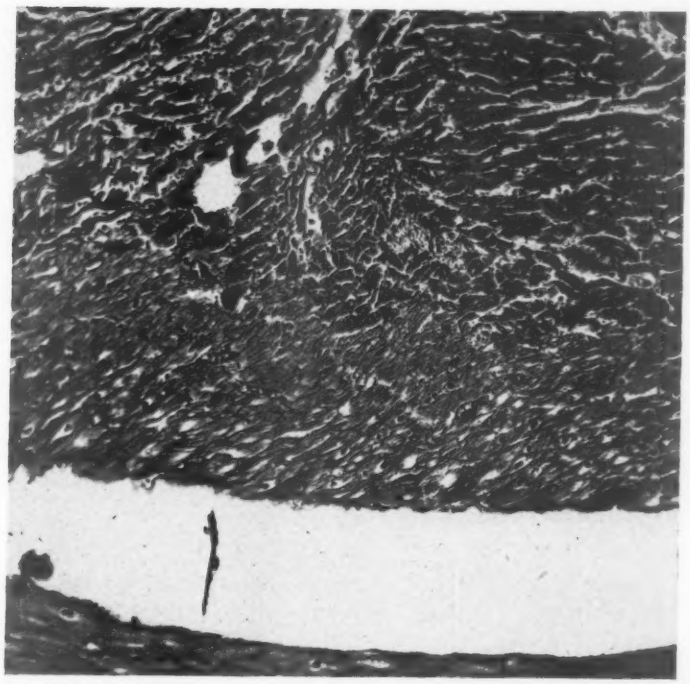

Fig. 2.—Photomicrograph of the myocardium showing the zone of unaffected muscle fibers directly beneath the endocardium. The fibers undergoing degeneration stain deeply with eosin and the striations are obscure (hematoxylin and eosin stain; magnification, ×120).

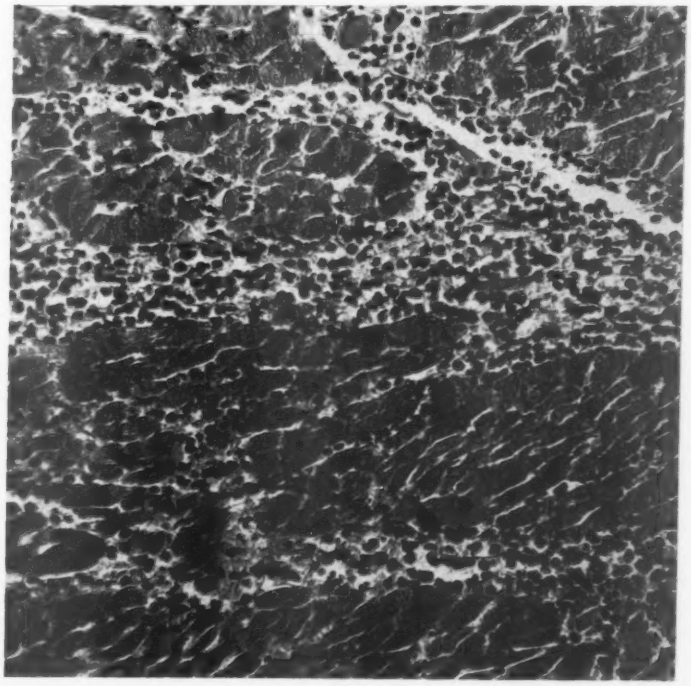

Fig. 3.—Photomicrograph of the myocardium. The muscle fibers are necrotic and the area infiltrated with polymorphonuclear leucocytes (hematoxylin and eosin stain; magnification, ×230).

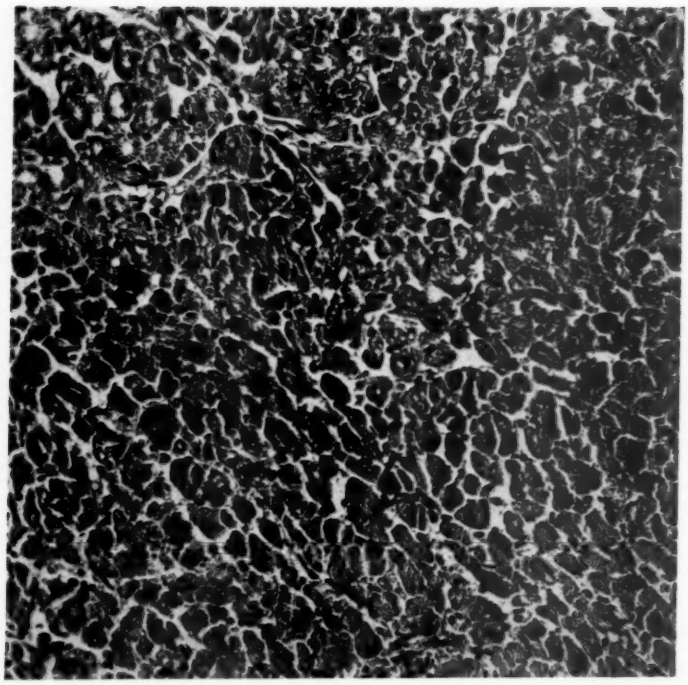

Fig. 4.—Photomicrograph of the myocardium. Early degenerative changes without inflammatory cell infiltration. The fibers in the central portion stain more deeply and the striations are obscure (hematoxylin and eosin stain; magnification, ×230).

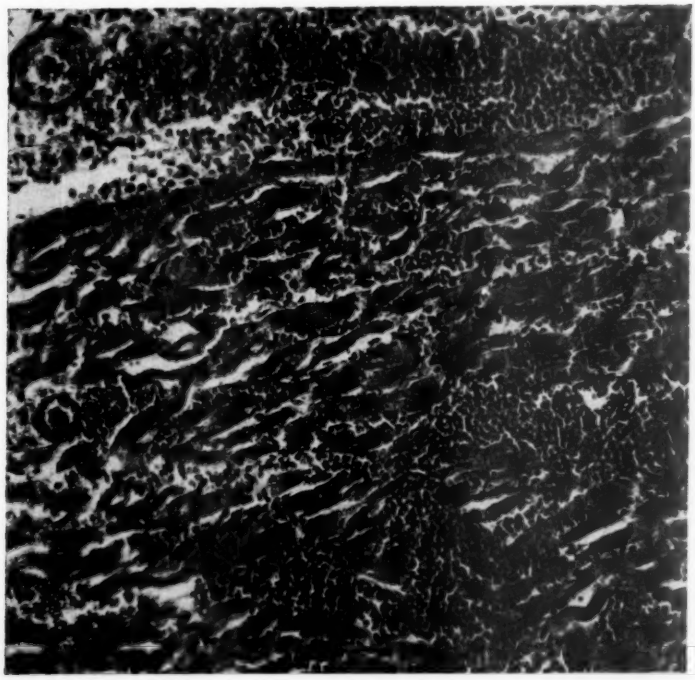

Fig. 5.—Photomicrograph of the myocardium. Note the hemorrhage between the muscle bundles and in the perivascular tissues. Degeneration of the muscle fibers is indicated by the loss of striations, granularity, thickened intercalated discs, and fragmentation (hematoxylin and eosin stain; magnification, ×230).

the relatively loose supporting tissue in the region of the large blood vessels. In some areas there was hyalinization of the muscle fibers associated with very little cellular infiltration (Fig. 4). In general, however, the degree of cellular infiltration was dependent upon the severity of the degenerative process. In many areas, marked hemorrhage was associated with degeneration and rupture of the muscle fibers (Fig. 5). There was no evidence of pre-existing disease.

Bacteriologic Studies.—No ante-mortem bacteriologic studies were made. Blood taken from the heart at autopsy was inoculated into brain broth, and no bacterial growth occurred. The splenic pulp was cultured on brain broth and was sterile. A block of myocardium, measuring about 1 sq. cm., was placed in acetone for one minute in order to destroy the contaminating surface organisms. It was then transferred to a sterile mortar and triturated with sterile sand and broth. Portions of this material were then inoculated into brain broth, Brewer's fluid thioglycollate medium, and upon a blood agar plate. A pure culture of micro-aerophylic *Streptococcus hemolyticus* was isolated. No contaminating organisms appeared in any of the media.

DISCUSSION

The various etiological agents which have been suggested as the cause of isolated myocarditis include the *Treponema pallidum*,[3] bacteria and bacterial toxins of an unknown type,[1, 2] a virus,[4] and *Staphylococcus citreus*.[5] Syphilis is admittedly responsible for a number of cases of myocarditis, but is certainly not the cause of the majority of cases of isolated myocarditis. None of the other agents have been proved to be responsible for the disease.

Among the cases reported in the literature, organisms were searched for in three cases. In the case reported by Rindfleisch,[5] *Staphylococcus citreus* was isolated from the myocardium. Abscesses were not found in the heart muscle, and hence its etiological relationship remains in doubt. In the other two cases reported by Scott and Saphir,[6] organisms were searched for by staining the tissue and not by culture. It is questionable whether this method of examination would reveal the presence of small numbers of organisms. Using a Gram's method which stains organisms very well in control tissues, we were unable to find organisms in the myocardium in our case.

The lesions in the myocardium are not unlike those which are caused by known infectious agents where the myocarditis is not the sole active inflammatory lesion.

In this case we know that the micro-aerophylic *Streptococcus hemolyticus* was the causative agent. It is hoped that the myocardium will be cultured in other instances. This procedure may reveal that isolated myocarditis is more commonly caused by an infectious agent than is now appreciated.

SUMMARY

1. A case of diffuse type of acute isolated myocarditis is reported.

2. A micro-aerophylic *Streptococcus hemolyticus* was isolated in pure culture from the myocardium. Cultures of the blood and spleen remained sterile.

3. Many cases of acute isolated myocarditis are probably due to an infectious agent, but the failure to recognize the condition clinically or grossly at necropsy has prevented proper bacteriologic studies.

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Abstracts and Reviews

Selected Abstracts

Mazer, M., and Reisinger, J. A.: An Electrocardiographic Study of Cardiac Aging Based on Records at Rest and After Exercise. Ann. Int. Med. **21**: 645, 1944.

The present study demonstrates but few significant differences between the electrocardiographs of males in the third and fifth decades. In tracings taken at rest, significant differences between the two age groups were found only in the frequency of Q waves in Lead III, the voltage of R waves in the limb leads, and the voltage of T waves in Leads I and II.

It has been found also that, though the alterations in the QRS complex due to exercise show definite average trends, there are individual variations in either direction. Hence, definite criteria for the normal variation of this component cannot be established. The changes after exercise in the S-T segment were more constant and the variations from the average were small. Except for the T wave in Lead I in one case, all of the T waves in Leads I, II, and IV were upright after exercise. Low voltage of the T waves in all of the limb leads or in the chest lead was not seen after exercise.

From the data of the present study the following criteria for an abnormal electrocardiographic response to standard exercise in the age groups considered are suggested:

1. Depression of the S-T segment (by exercise) of more than 0.75 mm. in Lead I, 1.5 mm. in Lead II, 0.75 mm. in Lead III, and 1.75 mm. in Lead CF_4.
2. Inversion of the T waves in Leads I, II, or CF_4.
3. Low voltage of the T waves in all of the limb leads.

McCULLOCH.

Kreutzer, R.: Further Experience in the Surgical Treatment of Persistence of the Ductus Arteriosus. Rev. argent. de cardiol. **11**: 240, 1944.

Four observations of ligation of the ductus arteriosus are presented. In two cases the results were optimal though some cardiovascular anomalies persisted. The murmurs disappeared. A third patient died four days after operation. No autopsy was made, but, from the clinical and radiological symptoms, death may be imputed to pulmonary atelectasia and purulent pleuropericarditis. In the fourth case the murmur which disappeared after ligation reappeared eight months later with the same characteristics, though less intense.

The author's observations are in line with Shapiro's opinion that operation should be performed only when the cases of persistent ductus arteriosus, not accompanied by other cardiac malformations, show signs of heart enlargement or insufficiency or, in their absence, of bacterial endocarditis.

AUTHOR.

Gilchrist, A. R.: Patent Ductus Arteriosus and Its Surgical Treatment. Brit. Heart J. **7**: 1, 1945.

Patency of the ductus arteriosus has been studied in a series of twenty-eight consecutive patients, fourteen of whom were submitted to surgical ligation.

In diagnosis, emphasis is placed on the almost pathognomonic sign—the continuous murmur of Gibson. In the absence of the characteristic murmur, the diagnosis can still be established by the detection of other signs which, taken together, are of almost equal value. In order of importance these are: pulmonary artery dilatation, increased pulse pressure at rest or after exercise, and a long harsh basal systolic murmur with an accentuated or reduplicated pulmonary second sound.

The defect is in the nature of an arteriovenous fistula. In patent ductus arteriosus the ventricular outputs are unequal, the left exceeding the right by the amount of flow through the ductus. This in turn is regulated, at least in part, by the size of the channel and the degree of resistance offered by the peripheral arterioles of the pulmonary circuit, the constriction of which decreases the burden thrown on the left ventricle by correcting the tendency to an excessive fall in diastolic pressure.

Most cases are observed in childhood, and 70 per cent are detected before the age of 20 years is reached. After this, the condition becomes increasingly rare. The scanty number of adults so affected can be explained on several grounds, such as death in youth, spontaneous closure of the ductus in childhood, or on the failure of the clinician and pathologist to look for this lesion systematically in older patients.

Of fourteen patients (Cases 15 to 28) in whom surgery was judged unnecessary or undesirable, the eldest was 49 and the youngest 5 years, with an average age of 20 years. Two died, one from intercurrent infection and one from subacute bacterial endarteritis. Slight deterioration in physical capacity was observed in three patients. Two women married and have borne families without undue distress. In one patient, a 6-year-old boy, the ductus closed spontaneously.

Of the fourteen patients submitted to surgery, distinct improvement in the general health and physical capacity was observed in six. Four obtained less benefit than anticipated, chiefly because complete obliteration of the ductus was not always obtained. Two patients died in the period after operation.

The diagnosis of the infected ductus is discussed. As an aid to its recognition, emphasis is placed on the value of repeated x-ray examinations. The radiological appearances are, on occasions, unique. The changing pattern of the heart and lungs makes a sequence so characteristic that the diagnosis of bacterial endarteritis of the ductus and pulmonary artery should seldom be missed.

Two patients submitted to surgery on account of bacterial endarteritis died. Death in each instance was attributed to massive pulmonary collapse.

Problems of the postoperative period are discussed. The occurrence of respiratory complications, recanalization of the ductus after ligation, the significance of a return of the Gibson murmur after operation, and the course of the blood pressure response are considered.

The selection of patients for surgery demands careful consideration. The main factors to bear in mind are the age of the patient and the degree of cardiac embarrassment. In general, the younger patient should be accepted for surgery when symptoms are minimal, in the hope that by ductal occlusion the child may grow and develop normally. In older patients, on account of the increasing operative hazards, surgery can be justified only when symptoms, being more severe, warrant the risk. In the presence of an infected ductus, ligation should be undertaken without delay at any age. AUTHOR.

Luisada, A. A., and Wolff, L.: The Significance of the Pulmonary Diastolic Murmur in Cases of Mitral Stenosis. Am. J. M. Sc. **209**: 204, 1945.

Three cases of mitral stenosis, two with associated interauricular septal defect, are described in which pulmonic insufficiency was constantly present and independent of congestive failure. None have died. Phonocardiographic records of the murmurs are included.

The clinical signs of pulmonary insufficiency and its differentiation from aortic insufficiency are reviewed from the literature and tabulated. Pulmonary insufficiency is not always transient and functional in cases of mitral stenosis with or without interauricular septal defect, but may be permanent and organic as in the cases here reported. The nature of the possible organic changes is discussed.

AUTHORS.

Levine, S. A.: Certain Observations Referring to Cardiac Murmurs and to Their Mode of Transmission. Arch. Inst. Cardiol. Mex. **14**: 150, 1945.

The speed of the blood in the cardiac cavities and in the large vessels is an important factor in the production of murmurs and in determining their intensity. It is responsible for the appearance of presystolic murmurs under similar conditions in cases of incipient mitral stenosis. The same factor is responsible for the systolic murmurs that occur in conditions such as anemia, hyperthyroidism, and fever.

In clinical explorations it is useful to grade the intensity of murmurs. For this purpose, one may designate as grade 1 the weakest murmurs, with grade 6 the strongest (those perceptible with the stethoscope at a short distance from the thoracic wall), and one may assign to murmurs of intermediate intensity the grades 2 to 5. Systolic murmurs of grade 3 or higher denote usually some organic disease or some other pathologic condition. Systolic murmurs of grade 1 and sometimes those of grade 2 are often present in healthy subjects. Weak murmurs may disappear during deep inspiration even when caused by cardiac disease.

Some murmurs may be perceived at the olecranon even when a cuff on the arm is inflated to a pressure higher than the systolic pressure of a patient. The intense murmurs of pulmonary stenosis, of an intraventricular communication, and of aortic stenosis or insufficiency may be transmitted to the elbow or to the carotid arteries; this fact proves that murmurs are not transmitted by the blood stream but propagate in all directions from their origin and are specially well conducted by bone.

The present teachings on the propagation of murmurs should be revised, and, in general, the study of the nature of murmurs requires more research. AUTHOR.

Peeples, G. S. T.: The Rheumatic Fever Program in South Carolina. J. South Carolina M. A. **40**: 205, 1944.

A brief description is given of the Rheumatic Fever Program under the provisions of the Service for Crippled Children of the Children's Bureaus Service. This program is one of those conducted in about nineteen states at the present time. The details will be of interest to those who are conducting similar programs or who are interested in their initiation.

McCULLOCH.

Lange, K., and Boyd, L. J.: The Functional Pathology of Experimental Frostbite and the Prevention of Subsequent Gangrene. Surg., Gynec. & Obst. **80**: 346, 1945.

The tissue alterations after exposure to severe cold are described, and the sequence of events as well as the vascular occlusion due to stasis is discussed. The sequence of functional changes after exposure to mild cold, as elicited by the fluorescein test, is described, and emphasis is placed upon the arteriolar spasm and decreased capillary permeability. These vascular changes are independent of central nervous system influences and seem to occur by axon reflexes.

Cold sufficient to solidify the exposed tissues causes a complete interruption of circulation during the exposure. This is always followed by a period of complete restoration of circulation and increased capillary permeability as evidenced by the fluorescein test. This period lasts for six to sixteen hours after exposure. This is the most promising period for therapeutic endeavors. The period of circulatory restoration is followed by one with arteriolar and capillary occlusion resulting from the formation of red blood cell clots. Gangrene of the associated area is the consequence. Heparin administered during the period of circulatory restoration prevented gangrene in sixteen rabbits whereas all controls had complete gangrene of the part. Five animals were exposed by freezing small areas; in the remaining animals the entire hind leg was frozen. Although tissue loss was averted by the early use of heparin, sensory and motor nerve paralysis was often not prevented.

Fourteen cases of human frostbite show that the fluorescein test permits the exact prediction of subsequent superficial tissue loss provided certain precautions are taken. Great surgical conservatism is in order in frostbite since these lesions show a marked tendency to heal. Moreover, the rules for amputation in occlusive vascular disease are not applicable in frostbite. After an injection of fluorescein the dye content of the blisters seems to afford a good insight into the vascular damage in the deeper structures. AUTHORS.

Woodbury, R. A., and Abreu, B. E.: Influence of Dying Gasps, Yawns and Sighs on Blood Pressure and Blood Flow. Am. J. Physiol. **142**: 721, 1944.

Gross and *net*, left and right ventricular pressures are recorded from dogs without operative entrance into the chest by means of hollow sounds inserted down the left carotid into the left ventricle and down the right jugular into the right ventricle.

Normal inspiration increases venous return to the right heart and produces contour changes characteristic of larger and more prolonged effective ejection without significantly changing the duration of systole.

Dying gasps, deep breathing, yawns, and sighs, which are generally considered as respiratory acts, markedly increase venous return. In the presence of cardiac arrest, dying gasps pump blood through the lungs and temporarily provide blood flow to the vital areas, the central nervous system, and the heart. Effective *net* pressure as great as 50 mm. Hg in the pulmonary artery, 50 mm. Hg in the coronary arteries, and 40 mm. Hg in the central nervous system arteries was created by dying gasps in dogs where cardiac action had ceased.

AUTHORS.

Altschule, M. D., Iglauer, A., and Zamcheck, N.: Respiration and Circulation in Patients With Obstruction of the Superior Vena Cava. Cerebral Factors in Dyspnea and Orthopnea. Arch. Int. Med. **75**: 24, 1945.

A study of the respiratory and cardiovascular dynamics in five patients with obstruction of the superior vena cava revealed that hyperventilation, with a consequent fall in alveolar carbon dioxide, often occurs in this syndrome. Stasis may be present in the brain of a patient with obstruction of the superior vena cava. High venous pressure and slowed circulation time do not necessarily indicate the presence of stasis. Studies of the blood gases are more helpful in this regard.

It is concluded that the occurrence of hyperventilation, dyspnea, orthopnea, or periodic breathing in a patient with obstruction of the superior vena cava is associated with tissue stasis in the brain.

AUTHORS.

Frank, H. A., Altschule, M.D., and Zamcheck, N.: Traumatic Shock. IX. Pressor Therapy: The Effect of Paredrine on the Circulation in Hemorrhagic Shock in Dogs. J. Clin. Investigation **24**: 54, 1945.

Vasoconstriction is not maximal in hemorrhagic shock in the dog; arterial and venous pressures can be raised for considerable periods of time by paredrine. The responsiveness to paredrine diminishes or is lost late in shock or after repeated dosage. The increase in arterial and venous pressures is not accompanied by an improvement in blood flow. The increase in alertness and activity following effective paredrine injection in shock is not explained. These experiments do not indicate whether the vasoconstrictor effect of paredrine during hemorrhagic shock exerts a useful or harmful effect.

AUTHORS.

Mylon, E., Cashman, C. W., Jr., and Winternitz, M. C.: The Relation of Adrenalin and of the Carotid Sinus to the Hyperglycemia of Shock. Am. J. Physiol. **142**: 638, 1944.

Hyperglycemia after hemorrhage varies in extent with the rate of blood loss. It can be prevented by quantitative replacement with Tyrode solution immediately after each blood withdrawal. The anoxia attained is independent of blood loss or of replacement with Tyrode solution and cannot be the cause of the elevated blood sugar. Carotid sinus or vertebral artery ligation does not influence hyperglycemia after hemorrhage. Adrenalin hyperglycemia is mild as compared with that of hemorrhage. Carotid sinus or vertebral artery ligation abolishes or minimizes the hyperglycemic response to adrenalin even when there is adequate liver glycogen as demonstrated by chemical assay or by response to bleeding. The dependence of adrenalin hyperglycemia upon this neural mechanism suggests that the lack of the hyperglycemic response to adrenalin after hypophysectomy may be a result of damage to this pathway rather than to absence of the gland. Insulin sensitivity also is increased after carotid sinus or vertebral artery ligation, but not to the extent that follows hypophysectomy. It may result from interference with adrenalin activity essential both for the restoration of blood sugar and for the decrease of the excitability of the central nervous system.

AUTHORS.

Kondo, B., and Katz, L. N.: Heart Size in Shock Produced by Venous Occlusion of the Hind Limbs of the Dog. Am. J. Physiol. **143**: 77, 1945.

Changes in heart size following the production of shock by bilateral venous occlusion of the hind limbs of the dog were studied by means of x-ray. X-ray films of the heart in the anteroposterior and left lateral positions were taken, retraced, and the shadow area determined by planimetry. In some experiments, heart rate was controlled by atropinization.

Control studies showed that a change of heart size of 5 per cent, if uniform and consistent, was probably significant, and a 10 per cent change was unequivocal.

The operative procedure employed led to a consistent decline in heart size greatest in the first hour. This decline was attributed to the loss of circulating blood volume as shock developed, the rate of loss lessening as the experiment progressed.

The rate of decline in heart size lessened after the first quarter of the postoperative survival and later the heart size did not change or even increased slightly. It is suggested that these later changes may be due, in part at least, to the development of myocardial ischemia as a result of the slowed rate of blood flow, shared by the coronary circuit, leading to a loss of cardiac tone.

AUTHORS.

Kleinberg, W., Swingle, W. W., and Hays, H. W.: Intramuscular Pressure Changes in Shock. Am. J. Physiol. **143**: 89, 1945.

Henderson's method was utilized for studying changes in intramuscular pressure under the following experimental conditions: (a) pentobarbital sodium anesthesia of long and short duration; (b) before and after intravenous injection of adrenalin; (c) following morphine plus pentobarbital sodium anesthesia; (d) fatal shock induced by four different procedures; and (e) sublethal hemorrhage without shock.

Pentobarbital sodium anesthesia of twelve hours' duration did not induce any greater change in intramuscular pressure than anesthesia lasting two to three hours. Adrenalin, administered by vein, raised both the blood pressure and intramuscular pressure, but the latter remained elevated long after the blood pressure had returned to normal. Morphine, followed by intravenously administered pentobarbital sodium, lowered both the arterial pressure and intramuscular pressure for several hours. Shock induced in deeply anesthetized dogs by (a) release of limb tourniquets; (b) application of a limb press; (c) trauma to muscle masses of the hind legs; and (d) gunshot injury was accompanied in all cases by marked fall in the intramuscular pressure. Sublethal hemorrhage, without shock representing 33 c.c. per kilogram of body weight, caused a sharp rise in intramuscular pressure which was maintained for several hours after spontaneous return of the blood pressure to normal. Reinfusion of heparinized whole blood in the hemorrhaged dogs resulted in decline of the intramuscular pressure to control levels.

AUTHORS.

Canzanelli, A., Guild, R., and Rapport, D.: Tourniquet Shock in the Rabbit. Am. J. Physiol. **143**: 97, 1945.

Shock was produced in the rabbit by occlusion of the circulation in the hind legs. After two hours of occlusion at room temperature, the survival time after tourniquet release was $3.8 = 0.6$ hours; after five hours of occlusion it was $1.7 = 0.4$ hour. Thus a technique with predictable results is offered for the study of shock. Tourniquet shock in the rabbit is not due to loss of fluid in the ligated legs. Chilling the tourniqueted legs more than tripled the average survival time in most experiments; in the remainder death was delayed as much as twenty-four hours. Dehydration and previous fasting did not affect the survival time.

AUTHORS.

Wiggers, H. C., Ingraham, R. C., and Dille, J.: Hemorrhagic-Hypotension Shock in Locally Anesthetized Dogs. Am. J. Physiol. **143**: 126, 1945.

Combined moderate and drastic hemorrhagic-hypotension of the intensity recommended for production of irreversible shock in anesthetized dogs induces this condition even more regularly in locally anesthetized dogs. Specifically, mortality was 100 per cent in our Series A dogs, even though only two of the thirteen dogs were permitted to endure the full 135-minute hypotension period. Under these conditions (a) postreinfusion survival times were shorter; (b) equivalent or smaller bleeding volumes were required to establish hypotension of equal intensity, and (c) the pathologic findings at autopsy were more extensive and intense than in a series of barbitalized dogs previously studied under these conditions. The conclusion was reached that (a) the barbitalized dog is equally if not better equipped to withstand the rigors of this procedure; (b) barbital anesthesia, per se, neither facilitates nor fosters the onset of shock when administered properly, and (c) a simplified and less severe shock producing procedure is desirable if a large series of shock experiments in locally anesthetized dogs is contemplated. It is suggested that psychic, emotional, or other neurogenic factors which frequently prevail under local

anesthesia as employed may partially account for the apparently greater susceptibility to the standardized hemorrhagic procedures observed in these experiments.

A less severe and less time consuming procedure was used in thirteen dogs (Series B) and was found more satisfactory. Irreversible shock was achieved in only 77 per cent of the animals; the others survived indefinitely. However, it is believed that shock can be attained in every instance by modifying the duration of the hypotension period. It appears that severe irreversible changes seldom develop until at least sixty minutes of hypotension (40 to 45 mm. Hg) have been endured.

In most of the nonsurviving dogs, a specific reaction was recognized which indicated that irreversible shock had been produced and that further continuance of the low arterial blood pressure period was unnecessary. Thus, once the blood pressure shows a persistent tendency to decline from the established hypotensive level, even immediate reinfusion of all withdrawn blood does not prevent eventual death from shock. It is considered doubtful that any remedial measures at present proposed for hemorrhagic conditions can do more than prolong the onset of death, once this reaction occurs.

Their dogs were at all times responsive to their environment, even in the advanced stage of hypotension. They never approached the moribund or comatose state until the terminal moments of the postreinfusion period as cardiorespiratory failure approached. Vomiting and/or bloody diarrhea were common occurrences in these dogs. This is mentioned inasmuch as Moon did not observe these phenomena in the uncomplicated hemorrhagic experiments he performed. Obviously, they are not distinctive features of shock dogs as differentiated from hemorrhaged dogs as Moon asserts.

The subjection of dogs, locally anesthetized, to an abbreviated (sixty minute) period of hypotension (40 to 45 mm. Hg) before reinfusion of all withdrawn blood will not induce shock in most instances; nine of ten dogs survived this procedure. By reinfusing various blood or plasma substitutes instead of the blood withdrawn, their relative efficiency in severe hemorrhagic conditions can be evacuated.

AUTHORS.

Walcott, W. W.: Blood Volume in Experimental Hemorrhagic Shock. Am. J. Physiol. **143**: 247, 1945.

Blood volume studies were carried out on twenty-three unanesthetized dogs in hemorrhagic shock produced by a single rapid bleeding. Determinations were made of the magnitude of the compensatory reserves involved in the early restoration of the blood volume. These reserves averaged 10.7 per cent of the control blood volume but ranged from 3 to 18 per cent. It was concluded that for dogs under these conditions the blood volume must be reduced by at least 40 per cent to lead to progressive fatal shock.

AUTHOR.

Walcott, W. W.: Standardization of Experimental Hemorrhagic Shock. Am. J. Physiol. **143**: 254, 1945.

A method is presented for the standardization of hemorrhagic shock in the unanesthetized dog. The method consists of the rapid determination of the bleeding volume followed immediately by infusion of 25 per cent of the blood collected. This procedure requires less than ten minutes. A fixed volume of 10 ml. is subsequently withdrawn at half-hour intervals. This method of bleeding invariably produces fatal hemorrhagic shock. In a series of thirty dogs on which this method was employed the survival time averaged three hours, forty-five minutes.

AUTHOR.

Scherer, J. H., and Howe, J. S.: Fatal Cardiac Tamponade Following Sternal Puncture. J. Lab. & Clin. Med. **30**: 453, 1945.

The second death from sternal puncture recorded in the literature and the first autopsy on such a case is reported. The cause of death was cardiac tamponade, due to hemorrhage from laceration of the right ventricle by the needle. AUTHORS.

Guerra, F.: Biometric Studies Concerning Digitalin. Arch. Inst. Cardiol. Mex. 14: 160, 1945.

The generic term, digitalin, includes digitalic substances which differ qualitatively and quantitatively. In view of their chemical complexity their metabolism in the organism differs, hence the discrepancies in the clinical activity of the several crystalline digitalins. The main objection to the method of intravenous perfusion in the cat (adopted by the Committee of Hygiene of the League of Nations, by the U.S.P. XII, and by the other pharmacopoeias) is that, although this method is acceptable for the preparations made out of *Digitalis purpurea* and *Digitalis thapsi*, it is not adequate for those derived from *Digitalis lanata*, for which it is necessary to consider the gastrovenous coefficient. Furthermore, the biologic response obtained with the standard of powdered leaves of digitalis is qualitatively and quantitatively different from that obtained with pure glucosides or with the so-called digitalins.

The statistical instability of the *cat unit* indicates the need of a reference standard for the digitalins which should be effective clinically when administered by different routes and should be sufficiently stable for accurate control. With the purpose of finding such a standard, five samples of pure digitalins were titrated: Digitalin (A and B) powder, American process; Digitalin (C) crystallized by the French process; Digitoxin (D), identified by some with the crystalline Digitaline of Nativelle; and Digitalinum (E) powder, German process. The method followed was that of the U.S.P. XII, using two groups of six cats for each sample and adjusting the technical details to those of the international collaborative assay of the standard of digitalis leaves.

As a basis for future discussion of an international standard for digitalin, special care was taken to develop the study in terms of the statistical theory of all-or-nothing reactions, which has been established precisely on digitalis by the speculations of Trevan, de Lind van Wijngaarden, Gaddum, and Fisher, and especially those of Bliss, based on calculations of maximum likelihood.

For each sample the following are described: cumulative frequency, use of probits and of logarithmic doses for the transformation of the curve into a straight line, standard deviations, variation coefficients, and tests of skewness and of kurtosis. A later analysis of variance discusses the variation within and between the several samples titrated, their error, and the consistency and homogeneity of the results. The relative potency of the samples studied is established using, as a comparative standard, the titration of the sample of digitalin D (digitoxin), because of its stability both from the technical and from the clinical standpoint.

AUTHOR.

Book Reviews

NEFROPATIA GRAVÍDICA: By Dr. José Reynaldo Marcondes, University of São Paulo, Brazil. São Paulo, 1944, 191 pages.

This monograph is based upon 80 observations on 79 cases, including 45 toxemias of pregnancy and 35 other hypertensive and renal syndromes.

Toxemia of pregnancy is considered as due to an endocrine unbalance caused by a placentogenic substance. This would cause diffuse angiospasm, with secondary renal ischemia. Whenever the latter persists too long, irreversible renal lesions occur.

The monograph fails to present any new data of interest, but is nevertheless a careful and complete study of the subject. Differential diagnosis and treatment are discussed in detail.

ALDO LUISADA.

HEART DISEASE: By Paul Dudley White, M.D., Lecturer in Medicine, Harvard Medical School, and Physician to the Massachusetts General Hospital, Boston. The Macmillan Co., New York, 1944, ed. 3, 976 pages plus index, 138 illustrations, $9.00.

The revision of this book is based on additions made during the six years since the previous edition. Its value is obviously enhanced by the additional clinical experiences of the author and the clinical judgment that comes from years of study and careful observations.

The more important additions and revisions pertain to the range of the normal heart, phonocardiography, precordial leads, ligation of the patent ductus arteriosus, present status of the treatment of subacute bacterial endocarditis, splanchnic resection for hypertension, intracardiac thrombosis, pulmonary thrombosis, and other vascular accidents. The results are in keeping with the high standards maintained in the past. The addition concerning the range of the normal heart is particularly deserving of mention, especially at present because of the help that it may afford in the determination of the fitness of young men for military service. As pointed out by the author, this subject has been grossly neglected in the past and thus is deserving of more attention in the future. The extensive bibliography continues to be one of the excellent features of the book.

This book is well known to the profession through the past editions and because of the prominent position long held by the author in this field. Thus a recommendation is not needed, but merely an announcement that a new edition is available.

FRED M. SMITH.

BLOQUEIOS DE RAMO EM CLÍNICA: By A. B. Benchimol, Assistente da Faculdade Nacional de Medicina, Rio de Janeiro. Livraria Atheneu, Rio de Janeiro, 1943, 149 pages, 83 illustrations.

This work is based upon a very extensive survey of the literature and on the study of forty cases of bundle branch block. The evolution of ideas on bundle branch block is followed through ample quotations and also by reproducing the original tracings of different authors from Lewis (1916) to the latest contributions.

After a chapter on diagnosis and classification, the author studies different types of bundle branch block by means of electrocardiography and other graphic methods. Special attention is given to precordial leads. Unstable, focal, and bilateral block and the Wolff-Parkinson-White syndrome are discussed in detail.

In the following chapter, modifications caused by myocardial infarction on electrocardiograms of bundle branch block are reviewed, and the influence of both ventricular hypertrophy and the position of the heart is discussed. In spite of the difficulties presented by the association of bundle branch block with the two above-mentioned conditions, diagnosis is possible. The clinical study is illustrated by electrocardiograms and phonocardiograms.

There is still a divergence of opinion on the interpretation of bundle branch block tracings, according to Benchimol, but multiple precordial leads help in doubtful cases. The view that most of the electrocardiographic changes thought to be characteristic of bundle branch block are void of any meaning is justly supported by the author; he accepts only prolongation of QRS as evidence of the lesion.

The importance of other graphic methods (phonocardiography, sphygmography, and phlebography) in revealing asynchronous contraction of the two ventricles is properly emphasized. Evidence of delayed contraction of one ventricle represents, after all, absolute proof of the existence of bundle branch block.

ALDO LUISADA.

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

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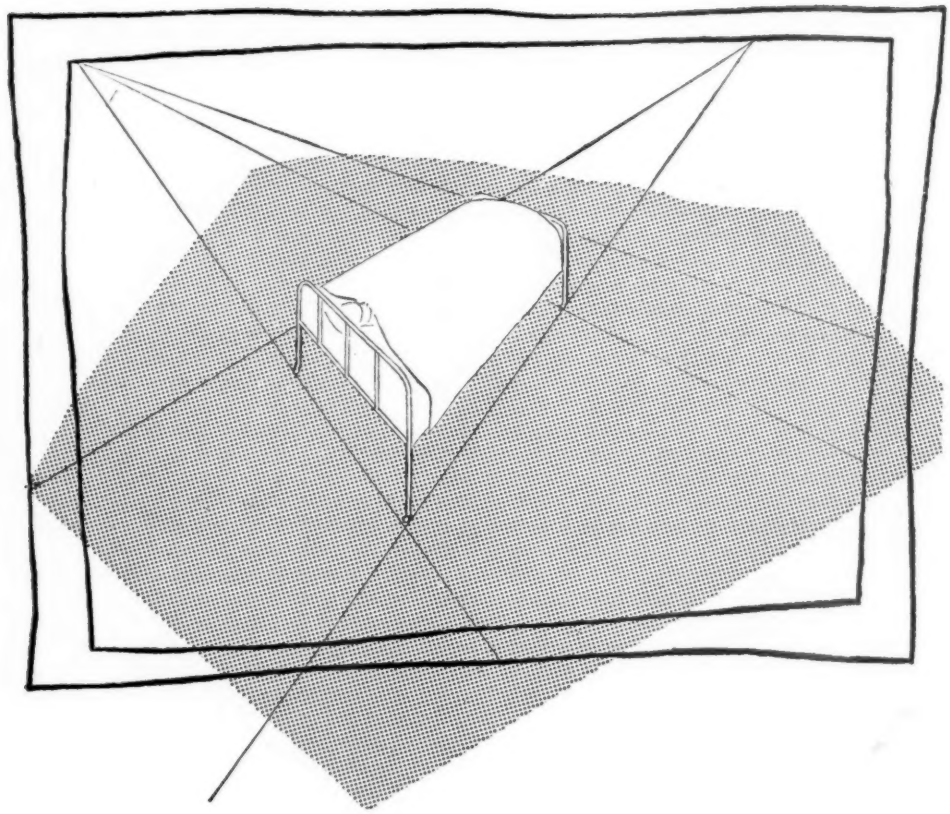

Perspective on Nutritive Therapy

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When the nutritive status of patients is severely affected, these four supportive measures have been used to good effect[4]:

1. *Diet:* High caloric, high protein diet, within the tolerance of the patient.
2. *Basic Therapy:* Prompt administration of thiamine, riboflavin, niacinamide *and* ascorbic acid *in dosage which clinical experience*[4, 5] *has shown to be effective* for the purpose.
3. *Natural B Complex:* Administration in large dosage.
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SQUIBB *Nutritive Agents*

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